

=> file registry
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STRUCTURE FILE UPDATES: 18 JUL 2006 HIGHEST RN 894196-03-3
DICTIONARY FILE UPDATES: 18 JUL 2006 HIGHEST RN 894196-03-3

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TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

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=> file hcaplus
FILE 'HCAPLUS' ENTERED AT 14:38:45 ON 19 JUL 2006
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FILE COVERS 1907 - 19 Jul 2006 VOL 145 ISS 4
FILE LAST UPDATED: 18 Jul 2006 (20060718/ED)

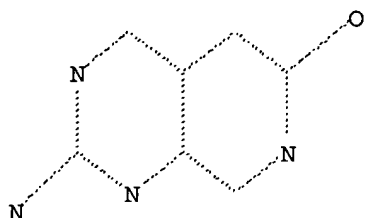
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This file contains CAS Registry Numbers for easy and accurate
substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> d stat que L33
L31 12 SEA FILE=HCAPLUS ABB=ON PLU=ON DEWDNEY N?/AU
L32 1091 SEA FILE=HCAPLUS ABB=ON PLU=ON GOLDSTEIN D?/AU
L33 3 SEA FILE=HCAPLUS ABB=ON PLU=ON L31 AND L32

=> d stat que L34
L3 STR



Structure attributes must be viewed using STN Express query preparation.

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L5          7 SEA FILE=REGISTRY SSS FUL L3
L6          2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5
L31         12 SEA FILE=HCAPLUS ABB=ON  PLU=ON  DEWDNEY N?/AU
L32        1091 SEA FILE=HCAPLUS ABB=ON  PLU=ON  GOLDSTEIN D?/AU
L34         1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L31 OR L32) AND L6
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=> d stat que L35

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L31         12 SEA FILE=HCAPLUS ABB=ON  PLU=ON  DEWDNEY N?/AU
L32        1091 SEA FILE=HCAPLUS ABB=ON  PLU=ON  GOLDSTEIN D?/AU
L35         23 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L31 OR L32) AND (P38/OBI OR
P 38/OBI)
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=> s L33-L35

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L45         23 (L33 OR L34 OR L35)
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=> file marpat

FILE 'MARPAT' ENTERED AT 14:39:29 ON 19 JUL 2006
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FILE CONTENT: 1961-PRESENT VOL 145 ISS 1 (20060714/ED)

SOME MARPAT RECORDS ARE DERIVED FROM INPI DATA FOR 1961-1987

MOST RECENT CITATIONS FOR PATENTS FROM MAJOR ISSUING AGENCIES
 (COVERAGE TO THESE DATES IS NOT COMPLETE):

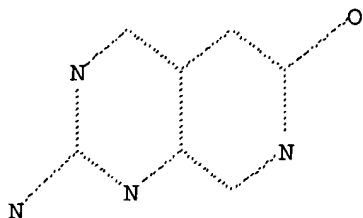
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US    2006118302 08 JUN 2006
DE 102004053653 04 MAY 2006
EP     1653548 03 MAY 2006
JP    2006112980 27 APR 2006
WO    2006053912 26 MAY 2006
GB     2419594 03 MAY 2006
FR     2877004 28 APR 2006
RU     2275374 27 APR 2006
CA     2518664 10 MAR 2006
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Expanded G-group definition display now available.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

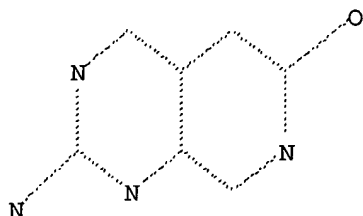
=> d stat que L39

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L3          STR
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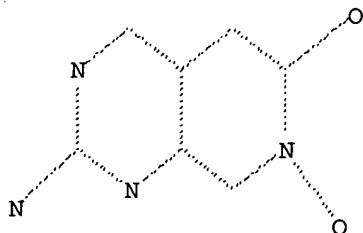
Structure attributes must be viewed using STN Express query preparation.

L15 54 SEA FILE=MARPAT SSS FUL L3
L19 STR



Structure attributes must be viewed using STN Express query preparation.

L21 13 SEA FILE=MARPAT SUB=L15 SSS FUL L19
L22 STR



Structure attributes must be viewed using STN Express query preparation.

L24 2 SEA FILE=MARPAT SUB=L15 SSS FUL L22
L31 12 SEA FILE=HCAPLUS ABB=ON PLU=ON DEWDNEY N?/AU
L32 1091 SEA FILE=HCAPLUS ABB=ON PLU=ON GOLDSTEIN D?/AU
L37 4 SEA FILE=MARPAT ABB=ON PLU=ON L31
L38 20 SEA FILE=MARPAT ABB=ON PLU=ON L32
L39 1 SEA FILE=MARPAT ABB=ON PLU=ON (L37 OR L38) AND (L21 OR L24)

=> file wpix

FILE 'WPIX' ENTERED AT 14:40:18 ON 19 JUL 2006
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FILE LAST UPDATED: 14 JUL 2006 <20060714/UP>
MOST RECENT DERWENT UPDATE: 200645 <200645/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,

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http://www.stn-international.de/stndatabases/details/ipc_reform.html and
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>>> FOR FURTHER DETAILS ON THE FORTHCOMING DERWENT WORLD PATENTS
INDEX ENHANCEMENTS PLEASE VISIT:
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<
'BIX' IS DEFAULT SEARCH FIELD FOR 'WPIX' FILE

=> d stat que L42

L40 4 SEA FILE=WPIX ABB=ON PLU=ON DEWDNEY N?/AU
L41 97 SEA FILE=WPIX ABB=ON PLU=ON GOLDSTEIN D?/AU
L42 3 SEA FILE=WPIX ABB=ON PLU=ON L40 AND L41

=> d stat que L43

L28 1 SEA FILE=WPIX ABB=ON PLU=ON (RAFUWH/DCN OR RAFUWI/DCN OR
RAFUWJ/DCN OR RAFUWK/DCN OR RAFUWL/DCN)
L29 1 SEA FILE=WPIX ABB=ON PLU=ON (979788-1-0-0/DCRE OR 979789-0-0-
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L30 1 SEA FILE=WPIX ABB=ON PLU=ON L28 OR L29
L40 4 SEA FILE=WPIX ABB=ON PLU=ON DEWDNEY N?/AU
L41 97 SEA FILE=WPIX ABB=ON PLU=ON GOLDSTEIN D?/AU
L43 1 SEA FILE=WPIX ABB=ON PLU=ON (L40 OR L41) AND L30

=> s L42-L43

L46 3 (L42 OR L43)

=> => dup rem L45 L46 L39

FILE 'HCAPLUS' ENTERED AT 14:41:05 ON 19 JUL 2006
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PROCESSING COMPLETED FOR L45
PROCESSING COMPLETED FOR L46
PROCESSING COMPLETED FOR L39

L47 24 DUP REM L45 L46 L39 (3 DUPLICATES REMOVED)
ANSWERS '1-23' FROM FILE HCAPLUS
ANSWER '24' FROM FILE WPIX

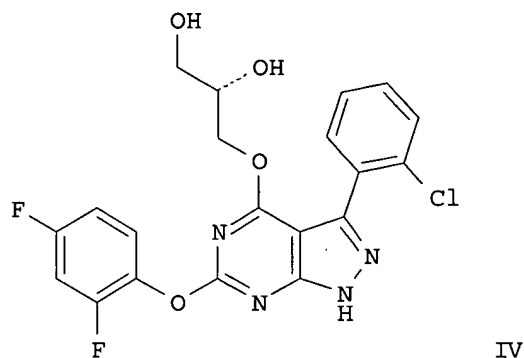
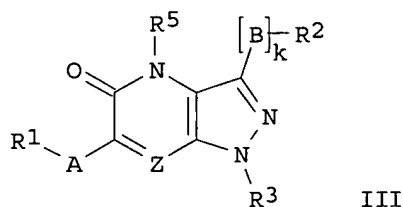
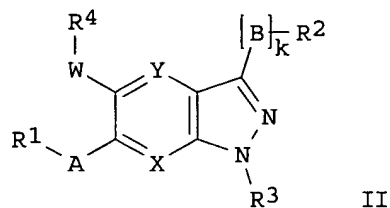
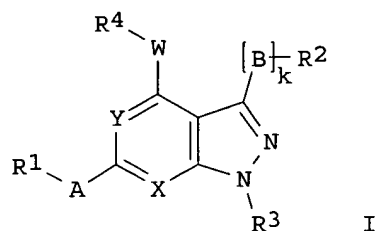
=> d ibib abs hitind hitstr L47 1-23; d ibib abs hitstr L47 24

L47 ANSWER 1 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2005:983769 HCAPLUS

DOCUMENT NUMBER: 143:286445
 TITLE: Preparation of fused pyrazolo pyrimidine and pyrazolo pyrimidinone derivatives as p38 kinase inhibitors
 INVENTOR(S): Arora, Nidhi; Billedeau, Roland Joseph; **Dewdney, Nolan James**; Gabriel, Tobias; **Goldstein, David Michael**; O'Yang, Counde; Soth, Michael
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 90 pp.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| US 2005197340 | A1 | 20050908 | US 2005-67336 | 20050225 |
| WO 2005085249 | A1 | 20050915 | WO 2005-EP1936 | 20050224 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |

PRIORITY APPLN. INFO.: US 2004-548583P P 20040227
 OTHER SOURCE(S): MARPAT 143:286445
 GI



AB The title compds. I-III [R1 = (hetero)aryl, aralkyl, cycloalkyl; R2 = (hetero)aryl, cycloalkyl, alkyl, heterocyclyl; R3 = H, alkyl; R4 = H, alkyl, OH, etc.; R5 = H, alkyl, heteroalkyl, etc.; X, Y = N, or one of X and Y = N and the other = CR6 (R6 = H, alkyl, OH, etc.); Z = N, CR6; W = O, SOm, CH2, (un)substituted NH; m = 0-2; A = O, CH2, SOm, C(O), etc.; B = O, SOm, C(O), etc.; k = 0-1], useful in treating p38 mediated disorders, were prepared and formulated. E.g., a multi-step synthesis of (S)-IV, starting from 4,6-dichloro-2-(methylthio)pyrimidine and 2-chlorobenzaldehyde, was given. The compds. I were found to be inhibitors of p38 MAP kinase. IV showed a p38 IC50 of 0.004 μ M.

IC ICM A61K031-519

ICS A61K031-498; C07D487-02

INCL 514249000; 514262100; 544256000; 544330000

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63

ST fused pyrazolo pyrimidinone prepn **p38** kinase inhibitor;
pyrazolopyrimidine prepn **p38** kinase inhibitor;
pyrazolopyrimidinone prepn **p38** kinase inhibitor

IT Inflammation

(Crohn's disease, treating; preparation of pyrazolopyrimidine and pyrazolopyrimidinone derivs. as **p38** kinase inhibitors)

IT Intestine, disease

(Crohn's, treating; preparation of pyrazolopyrimidine and pyrazolopyrimidinone derivs. as **p38** kinase inhibitors)

IT Respiratory distress syndrome

(adult, treating; preparation of pyrazolopyrimidine and pyrazolopyrimidinone derivs. as **p38** kinase inhibitors)

IT Lung, disease

(chronic obstructive pulmonary disease, treating; preparation of pyrazolopyrimidine and pyrazolopyrimidinone derivs. as **p38** kinase inhibitors)

IT Intestine, disease

(irritable bowel syndrome, treating; preparation of pyrazolopyrimidine and

pyrazolopyrimidinone derivs. as p38 kinase inhibitors)

IT Antiarthritics
(preparation of pyrazolopyrimidine and pyrazolopyrimidinone derivs. as p38 kinase inhibitors)

IT Arthritis
(treating; preparation of pyrazolopyrimidine and pyrazolopyrimidinone derivs. as p38 kinase inhibitors)

IT 165245-96-5, p38 Kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of pyrazolopyrimidine and pyrazolopyrimidinone derivs. as p38 kinase inhibitors)

IT 864299-82-1P 864300-75-4P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of pyrazolopyrimidine and pyrazolopyrimidinone derivs. as p38 kinase inhibitors)

IT 864298-62-4P 864298-63-5P 864298-64-6P 864298-66-8P 864298-68-0P
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864298-79-3P 864298-80-6P 864298-81-7P 864298-82-8P 864298-83-9P
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864300-81-2P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of pyrazolopyrimidine and pyrazolopyrimidinone derivs. as p38 kinase inhibitors)

IT 89-98-5, 2-Chlorobenzaldehyde 98-98-6, 2-Pyridinecarboxylic acid
367-27-1, 2,4-Difluorophenol 872-53-7, Cyclopentanecarboxaldehyde
918-05-8, N,N-Dimethyl methanesulfonamide 1979-98-2,
2-(Methylsulfanyl)pyrimidine-4,6-diol 2799-17-9, (S)-1-Amino-2-propanol
3512-17-2, 2,4,6-Trifluoropyridine 3900-89-8, 2-Chlorophenylboronic acid
4774-14-5, 2,6-Dichloropyrazine 5334-40-7 6299-25-8,
4,6-Dichloro-2-(methylthio)pyrimidine 14347-78-5 76513-69-4,
(2-Chloromethoxyethyl)trimethylsilane 449811-63-6 864301-27-9

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of pyrazolopyrimidine and pyrazolopyrimidinone derivs. as p38 kinase inhibitors)

IT 33097-11-9P 55864-87-4P 85426-79-5P 864300-82-3P 864300-83-4P
864300-84-5P 864300-85-6P 864300-86-7P 864300-87-8P 864300-88-9P
864300-89-0P 864300-90-3P 864300-91-4P 864300-92-5P 864300-93-6P
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864301-24-6P 864301-25-7P 864301-26-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of pyrazolopyrimidine and pyrazolopyrimidinone derivs. as p38 kinase inhibitors)

L47 ANSWER 2 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2004:878160 HCAPLUS

DOCUMENT NUMBER: 141:366244

TITLE: Preparation of substituted 7-azaquinazoline compounds as p38 kinase inhibitors

INVENTOR(S): Dewdney, Nolan James; Goldstein, David Michael

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 16 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| US 2004209903 | A1 | 20041021 | US 2004-824980 | 20040415 |
| AU 2004229163 | A1 | 20041028 | AU 2004-229163 | 20040413 |
| CA 2520785 | AA | 20041028 | CA 2004-2520785 | 20040413 |
| WO 2004091625 | A1 | 20041028 | WO 2004-EP3883 | 20040413 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, | | | | |

ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,
TD, TG

EP 1620105 A1 20060201 EP 2004-726958 20040413
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK

BR 2004009405 A 20060425 BR 2004-9405 20040413

CN 1774250 A 20060517 CN 2004-80009956 20040413

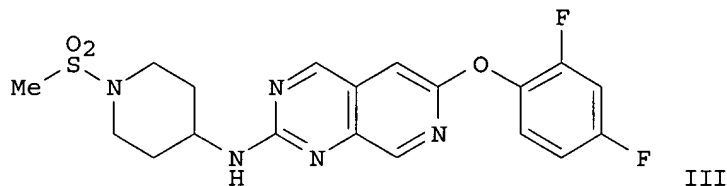
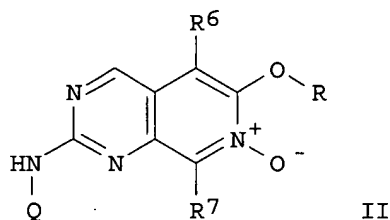
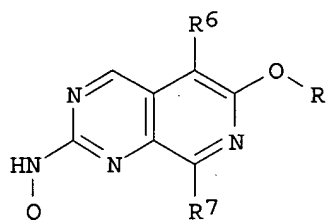
PRIORITY APPLN. INFO.:

US 2003-463229P P 20030416

WO 2004-EP3883 W 20040413

OTHER SOURCE(S): MARPAT 141:366244

GI



AB The title compds. [I or II; R = (un)substituted alkyl, cycloalkyl, aryl; R6 = H, alkyl; R7 = H, a non-interfering substituent such as alkyl, halo, etc.; Q = a non-aromatic moiety such as alkyl, cycloalkyl, heterocyclyl] which are useful as p38 kinase inhibitors, were prepared and formulated. E.g., a multi-step synthesis of III, starting from 2-chloro-4-methyl-5-nitropyridine, which showed IC50 of <0.05μM against p38 MAP kinase, was given.

IC ICM A61K031-519

ICS C07D487-02

INCL 514264110; 544280000

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1, 63

ST azaquinazoline prepn formulation **p38** MAP kinase inhibitor

IT Inflammation

(Crohn's disease, treating; preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

IT Intestine, disease

(Crohn's, treating; preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

IT Respiratory distress syndrome

(adult, treating; preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

IT Lung, disease

(chronic obstructive pulmonary disease, treating; preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

IT Heart, disease

(infarction, treating; preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

IT Anti-Alzheimer's agents
Antiarthritics
Antiasthmatics
Human
(preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

IT Inflammation
Spinal column, disease
(spondylitis, treating; preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

IT Brain, disease
(stroke, treating; preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

IT Alzheimer's disease
Arthritis
Asthma
Sepsis
(treating; preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

IT 165245-96-5, **p38** MAP kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

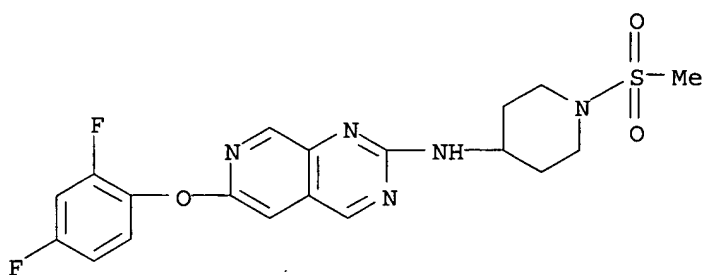
IT 777899-52-2P 777899-53-3P 777899-54-4P
777899-55-5P 777899-56-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

IT 367-27-1, 2,4-Difluorophenol 23056-33-9, 2-Chloro-4-methyl-5-nitropyridine 402927-97-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

IT 777899-57-7P 777899-58-8P 777899-59-9P 777899-60-2P 777899-61-3P
777899-62-4P 777899-63-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

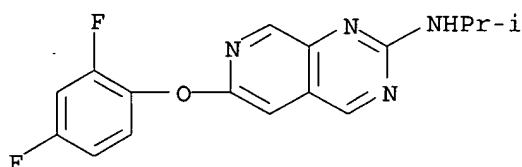
IT 777899-52-2P 777899-53-3P 777899-54-4P
777899-55-5P 777899-56-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of substituted 7-azaquinazoline compds. as **p38** kinase inhibitors)

RN 777899-52-2 HCAPLUS
CN 4-Piperidinamine, N-[6-(2,4-difluorophenoxy)pyrido[3,4-d]pyrimidin-2-yl]-1-(methylsulfonyl)- (9CI) (CA INDEX NAME)



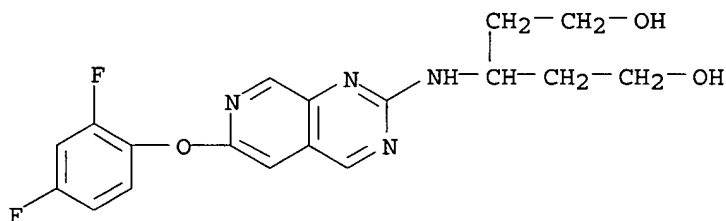
RN 777899-53-3 HCAPLUS

CN Pyrido[3,4-d]pyrimidin-2-amine, 6-(2,4-difluorophenoxy)-N-(1-methylethyl)-
(9CI) (CA INDEX NAME)



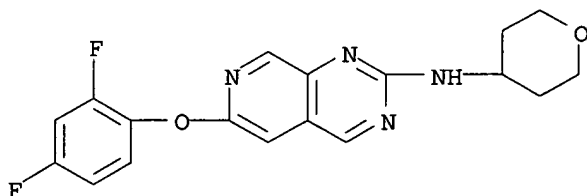
RN 777899-54-4 HCAPLUS

CN 1,5-Pentanediol, 3-[[6-(2,4-difluorophenoxy)pyrido[3,4-d]pyrimidin-2-yl]amino]- (9CI) (CA INDEX NAME)



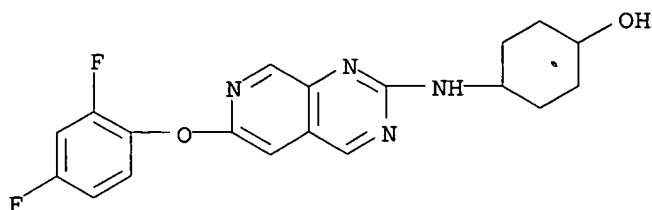
RN 777899-55-5 HCAPLUS

CN Pyrido[3,4-d]pyrimidin-2-amine, 6-(2,4-difluorophenoxy)-N-(tetrahydro-2H-pyran-4-yl)- (9CI) (CA INDEX NAME)



RN 777899-56-6 HCAPLUS

CN Cyclohexanol, 4-[[6-(2,4-difluorophenoxy)pyrido[3,4-d]pyrimidin-2-yl]amino]- (9CI) (CA INDEX NAME)



L47 ANSWER 3 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
 10
 ACCESSION NUMBER: 2006:123964 HCAPLUS
 DOCUMENT NUMBER: 144:369962
 TITLE: Discovery of S-[5-Amino-1-(4-fluorophenyl)-1H-pyrazol-4-yl]-[3-(2,3-dihydroxypropoxy)phenyl]methanone (RO3201195), an Orally Bioavailable and Highly Selective Inhibitor of p38 Map Kinase
 AUTHOR(S): Goldstein, David M.; Alfredson, Tom; Bertrand, Jay; Browner, Michelle F.; Clifford, Ken; Dalrymple, Stacie A.; Dunn, James; Freire-Moar, Jose; Harris, Seth; Labadie, Sharada S.; La Fargue, JoAnn; Lapierre, Jean Marc; Larrabee, Susan; Li, Fujun; Papp, Eva; McWeeney, Daniel; Ramesha, Chakk; Roberts, Rick; Rotstein, David; San Pablo, Bong; Sjogren, Eric B.; So, On-Yee; Talamas, Francisco X.; Tao, Will; Trejo, Alejandra; Villasenor, Armando; Welch, Mary; Welch, Teresa; Weller, Paul; Whiteley, Phyllis E.; Young, Kelly; Zipfel, Sheila
 CORPORATE SOURCE: Roche Palo Alto LLC, Palo Alto, CA, 94304, USA
 SOURCE: Journal of Medicinal Chemistry (2006), 49(5), 1562-1575
 CODEN: JMCMAR; ISSN: 0022-2623
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB A novel class of highly selective inhibitors of p38 MAP kinase was discovered from high throughput screening. The synthesis and optimization of a series of 5-amino-N-phenyl-1H-pyrazol-4-yl-3-phenylmethanones is described. An X-ray crystal structure of this series bound in the ATP binding pocket of unphosphorylated p38 α established the presence of a unique hydrogen bond between the exocyclic amine of the inhibitor and threonine 106 which likely contributes to the selectivity for p38. The crystallog. information was used to optimize the potency and physicochem. properties of the series. The incorporation of the 2,3-dihydroxypropoxy moiety on the pyrazole scaffold resulted in a compound with excellent drug-like properties including high oral bioavailability. These efforts identified RO3201195 as an orally bioavailable and highly selective inhibitor of p38 which was selected for advancement into Phase I clin. trials.
 CC 28-8 (Heterocyclic Compounds (More Than One Hetero Atom))
 Section cross-reference(s): 1
 IT Human
 (discovery of S-[5-Amino-1-(4-fluorophenyl)-1H-pyrazol-4-yl]-[3-(2,3-dihydroxypropoxy)phenyl]methanone (RO3201195), an orally bioavailable and highly selective inhibitor of p38 Map kinase)
 IT 165245-96-5, p38 Map kinase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (discovery of S-[5-Amino-1-(4-fluorophenyl)-1H-pyrazol-4-yl]-[3-(2,3-dihydroxypropoxy)phenyl]methanone (RO3201195), an orally bioavailable

- and highly selective inhibitor of **p38** Map kinase)
- IT 249936-55-8P
 RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
 (discovery of S-[5-Amino-1-(4-fluorophenyl)-1H-pyrazol-4-yl]-[3-(2,3-dihydroxypropoxy)phenyl]methanone (RO3201195), an orally bioavailable and highly selective inhibitor of **p38** Map kinase)
- IT 249936-11-6P 249936-69-4P 882175-25-9P 882175-29-3P 882175-38-4P
 RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
 (discovery of S-[5-Amino-1-(4-fluorophenyl)-1H-pyrazol-4-yl]-[3-(2,3-dihydroxypropoxy)phenyl]methanone (RO3201195), an orally bioavailable and highly selective inhibitor of **p38** Map kinase)
- IT 33064-14-1P 54606-37-0P 249935-58-8P 249935-59-9P 249935-60-2P
 249935-61-3P 249935-62-4P 249935-64-6P 249935-74-8P 249935-82-8P
 249936-01-4P 249936-10-5P 249936-33-2P 249936-38-7P 249936-41-2P
 249936-47-8P 249936-48-9P 249936-54-7P 882175-13-5P 882175-14-6P
 882175-15-7P 882175-16-8P 882175-17-9P 882175-18-0P 882175-19-1P
 882175-20-4P 882175-21-5P 882175-22-6P 882175-24-8P 882175-26-0P
 882175-27-1P 882175-28-2P 882175-32-8P 882175-33-9P 882175-34-0P
 882175-36-2P
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
 (discovery of S-[5-Amino-1-(4-fluorophenyl)-1H-pyrazol-4-yl]-[3-(2,3-dihydroxypropoxy)phenyl]methanone (RO3201195), an orally bioavailable and highly selective inhibitor of **p38** Map kinase)
- IT 75-05-8, Acetonitrile, reactions 89-25-8, 3-Methyl-1-phenyl-5-pyrazolone
 93-58-3, Methyl benzoate 94-05-3, Ethyl (ethoxymethylene)cyanoacetate
 98-88-4, Benzoyl chloride 100-63-0, Phenylhydrazine 107-19-7,
 Propargyl alcohol 109-01-3, 1-Methylpiperazine 110-89-4, Piperidine,
 reactions 371-14-2, 4-Fluorophenylhydrazine 529-27-1,
 2-Methylphenylhydrazine 540-51-2, 2-Bromoethanol 586-75-4,
 4-Bromobenzoyl chloride 614-16-4, Benzoylacetonitrile 618-89-3, Methyl
 3-bromobenzoate 619-27-2, 3-Nitrophenylhydrazine 619-44-3, Methyl
 4-iodobenzoate 622-15-1, N,N'-Diphenylformamidine 658-27-5,
 3-Fluorophenylhydrazine 1692-15-5, 4-Pyridinylboronic acid 1878-67-7,
 3-Bromophenylacetic acid 2127-03-9, 2,2'-Dipyridinyl disulfide
 2368-80-1, 2-Fluorophenylhydrazine 2386-58-5, Vinylsulfonamide
 3471-32-7, 4-Methoxyphenylhydrazine 3647-69-6, 4-(2-Chloroethyl)morpholine hydrochloride 5368-81-0, Methyl 3-methoxybenzoate
 18312-46-4, 2-Methoxyphenylhydrazine 19438-10-9, Methyl
 3-hydroxybenzoate 23735-43-5 23788-74-1 58313-23-8, Ethyl
 3-iodobenzoate 79629-41-7, 2-Bromoallyloxymethylbenzene 131534-65-1
 197958-29-5, 2-Pyridinylboronic acid 249937-07-3 747413-17-8
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (discovery of S-[5-Amino-1-(4-fluorophenyl)-1H-pyrazol-4-yl]-[3-(2,3-dihydroxypropoxy)phenyl]methanone (RO3201195), an orally bioavailable and highly selective inhibitor of **p38** Map kinase)
- IT 6123-64-4P 28229-69-8P, 2-(3-Bromophenyl)ethanol 70591-86-5P,
 3-Bromobenzoylacetonitrile 138907-68-3P 187949-90-2P 247206-80-0P
 249935-63-5P 249936-35-4P 249936-65-0P 249936-98-9P 249936-99-0P
 249937-00-6P 249937-02-8P 249937-03-9P 249937-08-4P 249937-09-5P
 249937-10-8P 249937-11-9P 249937-12-0P 249937-13-1P 249937-22-2P
 249937-23-3P 249937-25-5P 249937-44-8P 249937-47-1P 331777-15-2P
 882175-23-7P 882175-30-6P 882175-31-7P 882175-35-1P 882175-37-3P
 882175-39-5P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (discovery of S-[5-Amino-1-(4-fluorophenyl)-1H-pyrazol-4-yl]-[3-(2,3-

dihydroxypropoxy)phenyl]methanone (RO3201195), an orally bioavailable and highly selective inhibitor of p38 Map kinase)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 4 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1004746 HCAPLUS

DOCUMENT NUMBER: 143:306308

TITLE: Preparation of heteroaryl-fused pyrazolo derivatives as inhibitors of p38 kinase

INVENTOR(S): Arora, Nidhi; Billedeau, Roland J.; **Dewdney, Nolan James**; Gabriel, Tobias; **Goldstein, David Michael**; Soth, Michael; Trejo-Martin, Teresa Alejandra

PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.; McCaleb, Kristin Lynn

SOURCE: PCT Int. Appl., 73 pp.

CODEN: PIXXD2

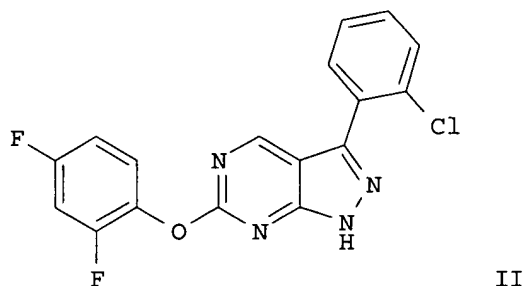
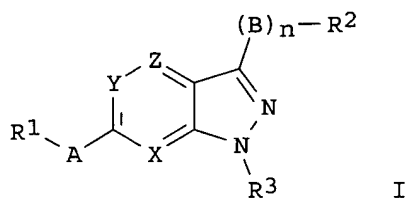
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--|----------|-----------------|------------|
| WO 2005085248 | A1 | 20050915 | WO 2005-EP1815 | 20050222 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | |
| RW: | BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| US 2005203091 | A1 | 20050915 | US 2005-65890 | 20050225 |
| PRIORITY APPLN. INFO.: | | | US 2004-548642P | P 20040227 |
| OTHER SOURCE(S): | MARPAT 143:306308 | | | |
| GI | | | | |



- AB Title compds. I [R1 = (un)substituted aryl, heteroaryl or cycloalkyl; R2 = (un)substituted aryl, heteroaryl, alkyl, etc.; R3 = H or alkyl; one or two of X, Y and Z is N, and the other is CR4; R4 independently = H, alkyl, halo, etc.; A = O, CO, CH2, etc.; n = 0-1; B = O, CO, CH=CH, etc.] and their pharmaceutically acceptable salts, are prepared and disclosed as inhibitors of p38 kinase. Thus, e.g., II was prepared by cyclization of (2-chlorophenyl)-(4-chloro-2-methylsulfanylpurimidin-5-yl)-methanone (preparation given) with hydrazine followed by oxidation to the resp. sulfonyl derivative and subsequent coupling with 2,4-difluorophenol. The inhibitory activity of I against p38 kinase was determined by measuring the transfer of the γ -phosphate from γ -33P-ATP by p38 kinase to Myelin Basic Protein (MBP) and it was revealed that compds. of the invention were inhibitors of p38 kinase, with one compound displaying an IC50 value of approx. 0.01 μ M. I as inhibitors of p38 kinase should prove useful in the treatment of arthritis, Crohn's disease or chronic obstructive pulmonary disease. Pharmaceutical compns. comprising I are disclosed.
- IC ICM C07D487-04
ICS C07D471-04; A61K031-4162; A61K031-4985; A61K031-519; A61P019-02; A61P025-28; C07D239-00; C07D231-00; C07D241-00
- CC 28-8 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63
- ST heteroaryl fused pyrazolo deriv prepn inhibitor p38 kinase
antiarthritic
- IT Inflammation
(Crohn's disease; preparation of heteroaryl-fused pyrazolo derivs. as inhibitors of p38 kinase)
- IT Intestine, disease
(Crohn's; preparation of heteroaryl-fused pyrazolo derivs. as inhibitors of p38 kinase)
- IT Respiratory distress syndrome
(adult; preparation of heteroaryl-fused pyrazolo derivs. as inhibitors of p38 kinase)

IT Lung, disease
(chronic obstructive pulmonary disease; preparation of heteroaryl-fused pyrazolo derivs. as inhibitors of p38 kinase)

IT Intestine, disease
(irritable bowel syndrome; preparation of heteroaryl-fused pyrazolo derivs. as inhibitors of p38 kinase)

IT Anti-inflammatory agents
(nonsteroidal; preparation of heteroaryl-fused pyrazolo derivs. as inhibitors of p38 kinase)

IT Alzheimer's disease
Anti-Alzheimer's agents
Antiarthritics
Arthritis
Inflammation
(preparation of heteroaryl-fused pyrazolo derivs. as inhibitors of p38 kinase)

IT 165245-96-5, p38 Kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of heteroaryl-fused pyrazolo derivs. as inhibitors of p38 kinase)

IT 864301-19-9P 864301-20-2P 864542-52-9P 864542-54-1P 864542-56-3P
864542-58-5P 864542-59-6P 864542-60-9P 864542-61-0P 864542-62-1P
864542-63-2P 864542-64-3P 864542-65-4P 864542-66-5P 864542-67-6P
864542-68-7P 864542-69-8P 864542-70-1P 864542-71-2P 864542-72-3P
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864542-78-9P 864542-79-0P 864542-80-3P 864542-81-4P 864542-82-5P
864542-83-6P 864542-84-7P 864542-85-8P 864542-86-9P 864542-87-0P
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864542-93-8P 864542-94-9P 864542-95-0P 864542-96-1P 864542-97-2P
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864543-08-8P 864543-09-9P 864543-10-2P 864543-11-3P 864543-12-4P
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RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
(Uses)
(preparation of heteroaryl-fused pyrazolo derivs. as inhibitors of p38 kinase)

IT 89-98-5, 2-Chlorobenzaldehyde 108-12-3, Isovaleryl chloride 122-51-0,
Triethyl orthoformate 348-54-9, 2-Fluoroaniline 367-25-9,
2,4-Difluoroaniline 367-27-1, 2,4-Difluorophenol 532-27-4,
2-Chloroacetophenone 1996-44-7, 2,4-Difluorothiophenol 2402-78-0,
2,6-Dichloropyridine 3900-89-8, 2-Chlorophenylboronic acid 4774-14-5,
2,6-Dichloropyrazine 16750-63-3, 2-Methoxyphenylmagnesium bromide
18368-64-4, 2-Chloro-5-methylpyridine 36082-50-5, 5-Bromo-2,4-
dichloropyrimidine 49844-90-8, 4-Chloro-2-(methylthio)pyrimidine
298709-29-2 679406-03-2, 4,6-Dichloropyridazine-3-carboxylic acid ethyl
ester
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of heteroaryl-fused pyrazolo derivs. as inhibitors of p38 kinase)

IT 20173-49-3P 60323-96-8P 60868-43-1P 205985-98-4P 864301-16-6P
864301-17-7P 864301-18-8P 864543-57-7P 864543-58-8P 864543-60-2P

864543-61-3P 864543-62-4P 864543-63-5P 864543-64-6P 864543-65-7P
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 864543-71-5P 864543-72-6P 864543-73-7P 864543-74-8P 864543-75-9P
 864543-76-0P 864543-77-1P 864543-78-2P 864543-79-3P 864543-80-6P
 864543-81-7P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

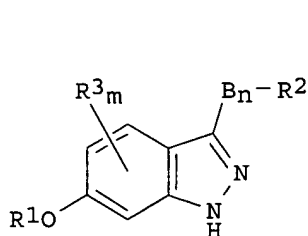
(preparation of heteroaryl-fused pyrazolo derivs. as inhibitors of p38 kinase)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

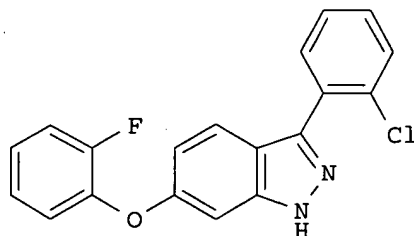
L47 ANSWER 5 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:1004715 HCAPLUS
 DOCUMENT NUMBER: 143:306306
 TITLE: Preparation of indazole derivatives as p38 MAP kinase inhibitors
 INVENTOR(S): Arora, Nidhi; Gabriel, Tobias; **Goldstein, David Michael**; Trejo-Martin, Teresa Alejandra
 PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.
 SOURCE: PCT Int. Appl., 39 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|-------------------|----------|-----------------|------------|
| WO 2005085206 | A1 | 20050915 | WO 2005-EP1816 | 20050222 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2005215595 | A1 | 20050929 | US 2005-65979 | 20050225 |
| PRIORITY APPLN. INFO.: | | | US 2004-548585P | P 20040227 |
| OTHER SOURCE(S): | MARPAT 143:306306 | | | |

GI



I



II

AB Title compds. represented by the formula I [wherein R₁, R₂ = independently

(hetero)aryl, aralkyl, cycloalkyl; m = 0-4; R₃ = H, (halo)alkyl, cyano, amino, etc.; n = 0 or 1; B = O, SO_j, CH(OR), (alkyl)amino or CO; j = 0-2; R = H or alkyl; and pharmaceutically acceptable salts, solvates or prodrugs thereof] were prepared as p38 MAP (Mitogen-activated protein) kinase inhibitors. For example, II was given in a multi-step synthesis starting from the reaction of 4-fluoro-2-nitrotoluene with 2-fluorophenol. 4-[6-(2-Fluorophenoxy)-1H-indazol-3-yl]phenol exhibited a p38 IC₅₀ (μM) of 0.028. Thus, I and their pharmaceutical compns. are useful for the treatment of p38 mediated disorders, such as arthritis, Crohns disease and irritable bowel syndrome, in a patient (no data).

- IC ICM C07D231-56
ICS A61K031-416; A61P025-28; A61P029-00
- CC 28-8 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63
- ST phenoxy aryl indazole prepn p38 MAP kinase inhibitor; arthritis
Crohn Alzheimer inflammation Lung disease treatment phenoxyindazole prepn
- IT Inflammation
(Crohn's disease; preparation of 6-phenoxy-indazole derivs. as p38 MAP kinase inhibitors)
- IT Intestine, disease
(Crohn's; preparation of 6-phenoxy-indazole derivs. as p38 MAP kinase inhibitors)
- IT Respiratory distress syndrome
(adult; preparation of 6-phenoxy-indazole derivs. as p38 MAP kinase inhibitors)
- IT Lung, disease
(chronic obstructive pulmonary disease; preparation of 6-phenoxy-indazole derivs. as p38 MAP kinase inhibitors)
- IT Intestine, disease
(irritable bowel syndrome; preparation of 6-phenoxy-indazole derivs. as p38 MAP kinase inhibitors)
- IT Alzheimer's disease
Anti-Alzheimer's agents
Anti-inflammatory agents
Antiarthritics
Arthritis
Human
Inflammation
(preparation of 6-phenoxy-indazole derivs. as p38 MAP kinase inhibitors)
- IT 165245-96-5, p38 MAP kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of 6-phenoxy-indazole derivs. as p38 MAP kinase inhibitors)
- IT 864500-29-8P, 6-(2-Fluorophenoxy)-3-phenyl-1H-indazole 864500-30-1P,
3-(2-Chlorophenyl)-6-(2-fluorophenoxy)-1H-indazole 864500-31-2P,
6-(2-Fluorophenoxy)-3-(3-methoxyphenyl)-1H-indazole 864500-32-3P,
6-(2-Fluorophenoxy)-3-(4-methoxyphenyl)-1H-indazole 864500-33-4P,
3-(5-Bromo-2-methoxyphenyl)-6-(2-fluorophenoxy)-1H-indazole
864500-34-5P, 6-(2-Fluorophenoxy)-3-(thiophen-3-yl)-1H-indazole
864500-35-6P, 6-(2-Fluorophenoxy)-3-(o-tolyl)-1H-indazole 864500-36-7P,
6-(2-Fluorophenoxy)-3-(4-methoxy-2-methylphenyl)-1H-indazole
864500-37-8P, 3-(Benzo[b]thiophen-3-yl)-6-(2-fluorophenoxy)-1H-indazole
864500-38-9P, 6-(2-Fluorophenoxy)-3-(2-methoxyphenyl)-1H-indazole
864500-39-0P, 3-(2,5-Dimethoxyphenyl)-6-(2-fluorophenoxy)-1H-indazole
864500-40-3P, 3-(2-Chlorophenyl)-5-(2-fluorophenoxy)-1H-indazole
864500-41-4P 864500-42-5P, 6-(2-Fluorophenoxy)-3-(furan-3-yl)-1H-indazole
864500-43-6P, 3-(3-Benzoyloxyphenyl)-6-(2-fluorophenoxy)-1H-indazole
864500-44-7P, 3-(3-Chloro-4-propoxyphenyl)-6-(2-fluorophenoxy)-1H-indazole
864500-45-8P, 6-(2-Fluorophenoxy)-3-(3-isopropoxyphenyl)-1H-

indazole 864500-46-9P, 3-(3,5-Dimethylphenyl)-6-(2-fluorophenoxy)-1H-indazole 864500-47-0P, [4-[6-(2-Fluorophenoxy)-1H-indazol-3-yl]phenyl]dimethylamine 864500-48-1P, 6-(2-Fluorophenoxy)-3-(4-isopropoxyphenyl)-1H-indazole 864500-49-2P, 3-(Benzo[b]thiophen-2-yl)-6-(2-fluorophenoxy)-1H-indazole 864500-50-5P, 6-(2-Fluorophenoxy)-3-(2-trifluoromethylphenyl)-1H-indazole 864500-51-6P, 6-(2-Fluorophenoxy)-3-(m-tolyl)-1H-indazole 864500-52-7P, 6-(2-Fluorophenoxy)-3-(p-tolyl)-1H-indazole 864500-53-8P, 3-(4-Chlorophenyl)-6-(2-fluorophenoxy)-1H-indazole 864500-54-9P, 3-(Biphenyl-4-yl)-6-(2-fluorophenoxy)-1H-indazole 864500-55-0P, 6-(2-Fluorophenoxy)-3-(1H-indol-3-yl)-1H-indazole 864500-56-1P, 3-(3-Chlorophenyl)-6-(2-fluorophenoxy)-1H-indazole 864500-57-2P, 3-(3,4-Dimethoxyphenyl)-6-(2-fluorophenoxy)-1H-indazole 864500-58-3P, 3-(4-Bromophenyl)-6-(2-fluorophenoxy)-1H-indazole 864500-59-4P, 6-(2-Fluorophenoxy)-3-(3,4,5-trimethoxyphenyl)-1H-indazole 864500-60-7P, 6-(2-Fluorophenoxy)-3-[4-(pyridin-3-yl)phenyl]-1H-indazole 864500-61-8P, N-[6-(2-Fluorophenoxy)-1H-indazol-3-yl]phenylamine 864500-62-9P, 4-[6-(2-Fluorophenoxy)-1H-indazol-3-yl]phenol
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 6-phenoxy-indazole derivs. as p38 MAP kinase inhibitors)

IT 367-12-4, 2-Fluorophenol 446-10-6, 4-Fluoro-2-nitrotoluene 3900-89-8, 2-Chlorophenylboronic acid

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of 6-phenoxy-indazole derivs. as p38 MAP kinase inhibitors)

IT 864500-63-0P, 4-(2-Fluorophenoxy)-2-nitrotoluene 864500-64-1P, [5-(2-Fluorophenoxy)-2-methylphenyl]amine 864500-65-2P, 6-(2-Fluorophenoxy)-1H-indazole 864500-66-3P, 6-(2-Fluorophenoxy)-3-iodo-1H-indazole 864500-67-4P, 6-(2-Fluorophenoxy)-3-iodoindazole-1-carboxylic acid tert-butyl ester 864500-68-5P, 3-(2-Chlorophenyl)-6-(2-fluorophenoxy)indazole-1-carboxylic acid tert-butyl ester

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of 6-phenoxy-indazole derivs. as p38 MAP kinase inhibitors)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 6 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:431405 HCAPLUS

DOCUMENT NUMBER: 142:482053

TITLE: Preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating p38 kinase mediated disorders

INVENTOR(S): Goldstein, David Michael

PATENT ASSIGNEE(S): Roche Palo Alto Llc, USA

SOURCE: U.S. Pat. Appl. Publ., 36 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------|----------|-----------------|----------|
| US 2005107408 | A1 | 20050519 | US 2004-987656 | 20041112 |
| AU 2004289428 | A1 | 20050526 | AU 2004-289428 | 20041104 |
| CA 2544247 | AA | 20050526 | CA 2004-2544247 | 20041104 |

WO 2005047284 A1 20050526 WO 2004-EP12475 20041104

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

US 2003-519789P

P 20031113

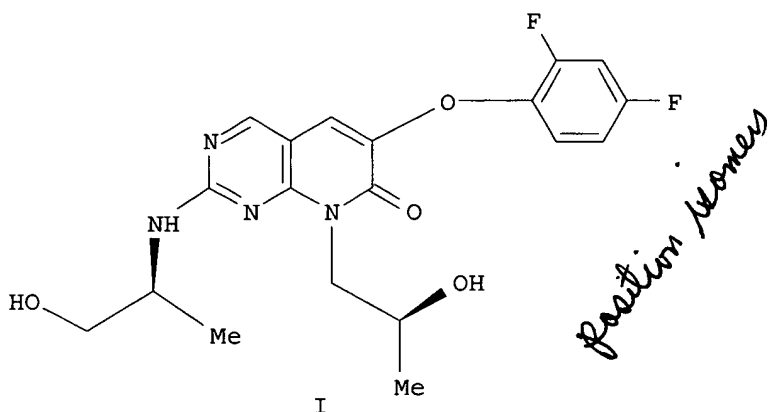
WO 2004-EP12475

W 20041104

OTHER SOURCE(S):

MARPAT 142:482053

GI



AB Compds. such as I were prepared for treating p38 mediated disorders in a patient. I was prepared starting from Et 4-chloro-2-methylthiopyrimidine-5-carboxylate and (S)-1-amino-2-propanol and involving a number of intermediates. I and other compds. were evaluated using a p38 mitogen-activated protein kinase in vitro assay.

IC ICM A61K031-519

ICS C07D487-02

INCL 514264110; 544279000

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))

ST hydroxyalkyl pyridopyrimidinone deriv prepn p38 kinase mediated disorder

IT Inflammation

(Crohn's disease; preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating p38 kinase mediated disorders)

IT Intestine, disease

(Crohn's; preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating p38 kinase mediated disorders)

IT Respiratory distress syndrome

(adult; preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating p38 kinase mediated disorders)

IT Intestine, disease

(irritable bowel syndrome; preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating p38 kinase mediated disorders)

IT Lung, disease
(obstructive; preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating p38 kinase mediated disorders)

IT Alzheimer's disease
Antiarthritics
(preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating p38 kinase mediated disorders)

IT 165245-96-5
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors; preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating p38 kinase mediated disorders)

IT 449808-64-4 449809-71-6 449809-86-3 449809-99-8 449810-69-9
449811-01-2 449811-92-1 851885-74-0 851885-75-1 851885-76-2
851885-77-3 851885-78-4 851885-79-5 851885-80-8 851885-81-9
851885-82-0 851885-83-1 851885-84-2 851885-85-3 851885-86-4
851885-87-5 851885-88-6
RL: PAC (Pharmacological activity); BIOL (Biological study)
(preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating p38 kinase mediated disorders)

IT 851885-55-7P 851885-56-8P 851885-57-9P 851885-58-0P 851885-59-1P
851885-60-4P 851885-61-5P 851885-62-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating p38 kinase mediated disorders)

IT 124-68-5 717-30-6 2749-11-3, (S)-2-Amino-1-propanol 2799-17-9,
(S)-1-Amino-2-propanol 5909-24-0, Ethyl 4-chloro-2-methylthiopyrimidine-5-carboxylate
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating p38 kinase mediated disorders)

IT 2799-16-8P 35320-23-1P 851885-63-7P 851885-64-8P 851885-65-9P
851885-66-0P 851885-67-1P 851885-68-2P 851885-69-3P 851885-70-6P
851885-71-7P 851885-72-8P 851885-73-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating p38 kinase mediated disorders)

IT 851885-89-7 851885-90-0 851885-91-1 851885-92-2 851885-93-3
851885-94-4 851885-95-5 851885-96-6 851885-97-7 851885-98-8
851885-99-9 851886-00-5 851886-01-6 851886-02-7 851886-03-8
851886-04-9 851886-05-0 851886-06-1 851886-07-2 851886-08-3
851886-09-4 851886-10-7 851886-11-8 851886-12-9 851886-13-0
851886-14-1 851886-15-2 851886-16-3 851886-17-4 851886-18-5
851886-19-6 851886-20-9 851886-21-0 851886-22-1
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of hydroxyalkyl substituted pyrido-7-pyrimidin-7-ones for treating p38 kinase mediated disorders)

L47 ANSWER 7 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1131486 HCAPLUS

DOCUMENT NUMBER: 143:431843

TITLE: Pathway to the clinic: Inhibition of P38 MAP kinase. A review of ten chemotypes selected for development

AUTHOR(S): Goldstein, David M.; Gabriel, Tobias

CORPORATE SOURCE: Department of Medicinal Chemistry, Roche Palo Alto,
Palo Alto, CA, 94304, USA
SOURCE: Current Topics in Medicinal Chemistry (Sharjah, United
Arab Emirates) (2005), 5(10), 1017-1029
CODEN: CTMCCL; ISSN: 1568-0266
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. P38 mitogen activated protein (MAP) kinase remains the most
compelling therapeutic target for oral drug intervention for a wide range
of autoimmune disorders based on the central role this enzyme plays in
inflammatory cell signaling. Efforts to discover inhibitors of p38
suitable for clin. investigation have continued to escalate in part due to
the incredible diversity of unique chemotypes reported to inhibit the
enzyme. Since 1993, at least seventeen p38 inhibitors have been reported
to have entered into clin. trials. Next generation inhibitors have been
disclosed with improved potency for p38 and enhanced selectivity vs. other
protein kinases. Over the last three years, there have been multiple
reports of cytokine suppression in humans following oral administration of
p38 inhibitors. These results, in addition to proof of concept studies in
rheumatoid patients, have established p38 inhibition as an avenue for the
future management of pro-inflammatory cytokine based diseases. This
review describes the discovery at Roche of novel p38 inhibitors which have
advanced into clin. trials. The pharmacol. of the Roche compds. is then
compared with eight chemical distinct p38 inhibitors known to have entered
clin. development.

CC 1-0 (Pharmacology)

IT Autoimmune disease

Drug design

Drug discovery

Drug targets

Human

(development P38 MAP kinase inhibitors)

IT Drug delivery systems

(oral; development P38 MAP kinase inhibitors)

IT Structure-activity relationship

(p38 MAPK inhibiting; development P38 MAP kinase
inhibitors)

IT 165245-96-5, P38 MAP kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(inhibitor; development P38 MAP kinase inhibitors)

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 8 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:143149 HCAPLUS

DOCUMENT NUMBER: 140:199338

TITLE: Preparation of 6-alkoxy-pyridopyrimidines as p
-38 MAP kinase inhibitors

INVENTOR(S): Goldstein, David Michael; Lim, Julie Anne

PATENT ASSIGNEE(S): F. Hoffmann-La Roche Ag, Switz.

SOURCE: PCT Int. Appl., 55 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

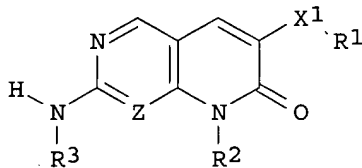
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

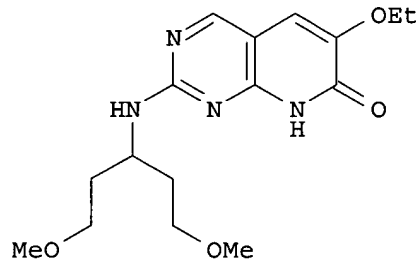
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|------|-------|-----------------|-------|
| ----- | ---- | ----- | ----- | ----- |

WO 2004014907 A1 20040219 WO 2003-EP8357 20030729
 W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
 CA 2492112 AA 20040219 CA 2003-2492112 20030729
 AU 2003251661 A1 20040225 AU 2003-251661 20030729
 EP 1539755 A1 20050615 EP 2003-784102 20030729
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
 BR 2003013297 A 20050621 BR 2003-13297 20030729
 CN 1675207 A 20050928 CN 2003-818688 20030729
 JP 2006507236 T2 20060302 JP 2004-526812 20030729
 US 2004038999 A1 20040226 US 2003-634936 20030805
 US 6965030 B2 20051115
 US 2005203300 A1 20050915 US 2005-121862 20050504
 PRIORITY APPLN. INFO.: US 2002-401491P P 20020806
 GI WO 2003-EP8357 W 20030729
 US 2003-634936 A3 20030805
 OTHER SOURCE(S): MARPAT 140:199338
 GI

*position isomer
see cited #N refs*



I



II

AB The title compds. [I; R1 = alkyl, cycloalkyl, cycloalkylalkyl, or CH2(alkenyl); X1 = O, NH, N(alkyl), S, CO; Z = N, CH; R2 = H, alkyl, cycloalkyl, etc.; R3 = alkyl, haloalkyl, aryl, etc.], were prepared E.g., a 3-step synthesis of II (starting from 4-amino-2-butylsulfanyl-4,5-dihydropyrimidine-5-carboxaldehyde and Et ethoxyacetate) which showed IC50 of about 7.7 μ M in p38 MAP kinase in vitro assay, was given. The pharmaceutical composition comprising the compound I is claimed.

IC ICM C07D471-04
 ICS A61K031-519; A61P029-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
 Section cross-reference(s): 1, 63

ST alkoxy pyridopyrimidine prepn p38 MAP kinase inhibitor;
 pyridopyrimidine alkoxy prepn p38 MAP kinase inhibitor

IT Inflammation
 (Crohn's disease, treatment of; preparation of 6-alkoxy-pyridopyrimidines as p-38 MAP kinase inhibitors)

IT Intestine, disease
 (Crohn's, treatment of; preparation of 6-alkoxy-pyridopyrimidines as p-38 MAP kinase inhibitors)

- IT Respiratory distress syndrome
(adult, treatment of; preparation of 6-alkoxy-pyridopyrimidines as p-38 MAP kinase inhibitors)
- IT Inflammation
Spinal column, disease
(ankylosing spondylitis, treatment of; preparation of 6-alkoxy-pyridopyrimidines as p-38 MAP kinase inhibitors)
- IT Lung, disease
(chronic obstructive pulmonary disease, treatment of; preparation of 6-alkoxy-pyridopyrimidines as p-38 MAP kinase inhibitors)
- IT Intestine, disease
(inflammatory, treatment of; preparation of 6-alkoxy-pyridopyrimidines as p-38 MAP kinase inhibitors)
- IT Intestine, disease
(irritable bowel syndrome, treatment of; preparation of 6-alkoxy-pyridopyrimidines as p-38 MAP kinase inhibitors)
- IT Anti-Alzheimer's agents
Anti-inflammatory agents
Antiasthmatics
Antirheumatic agents
Human
(preparation of 6-alkoxy-pyridopyrimidines as p-38 MAP kinase inhibitors)
- IT Arthritis
(psoriatic arthritis, treatment of; preparation of 6-alkoxy-pyridopyrimidines as p-38 MAP kinase inhibitors)
- IT Alzheimer's disease
Asthma
Psoriasis
Rheumatoid arthritis
(treatment of; preparation of 6-alkoxy-pyridopyrimidines as p-38 MAP kinase inhibitors)
- IT 165245-96-5, p38 MAP kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of 6-alkoxy-pyridopyrimidines as p-38 MAP kinase inhibitors)
- IT 661450-66-4P 661450-67-5P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of 6-alkoxy-pyridopyrimidines as p-38 MAP kinase inhibitors)
- IT 661450-62-0P 661450-63-1P 661450-64-2P 661450-65-3P 661450-68-6P
661450-69-7P 661450-70-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 6-alkoxy-pyridopyrimidines as p-38 MAP kinase inhibitors)
- IT 817-95-8, Ethyl ethoxyacetate 2032-34-0, 3,3-Diethoxypropanenitrile
5909-24-0, Ethyl 4-chloro-2-methylthiopyrimidine-5-carboxylate
6290-49-9, Methyl methoxyacetate 28177-48-2, 2,6-Difluorophenol
38041-19-9, 4-Aminotetrahydropyran 58859-46-4, Ethyl
4-amino-1-piperidinecarboxylate 661450-77-7 661450-78-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of 6-alkoxy-pyridopyrimidines as p-38 MAP kinase inhibitors)
- IT 770-31-0P, 4-Amino-2-(methylthio)pyrimidine-5-carboxaldehyde
17759-30-7P, 4-Methylamino-2-methylthiopyrimidine-5-methanol

76360-82-2P, Ethyl 4-(methylamino)-2-(methylthio)pyrimidine-5-carboxylate
 102669-01-2P 105161-35-1P 185040-32-8P, 4-Methylamino-2-methylthiopyrimidine-5-carboxaldehyde 185040-33-9P 185040-34-0P
 185040-35-1P, 4-Ethylamino-2-methylthiopyrimidine-5-carboxaldehyde
 449808-49-5P 449810-42-8P 449811-11-4P 661450-71-1P 661450-72-2P
 661450-73-3P 661450-74-4P 661450-75-5P 661450-76-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of 6-alkoxy-pyridopyrimidines as p-38 MAP kinase inhibitors)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 9 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:878161 HCAPLUS

DOCUMENT NUMBER: 141:366245

TITLE: Preparation of substituted quinazolines as p38 kinase inhibitors

INVENTOR(S): Dunn, James Patrick; Goldstein, David Michael; Stahl, Christoph Martin; Trejo-Martin, Teresa Alejandra

PATENT ASSIGNEE(S): F. Hoffmann-La Roche AG, USA

SOURCE: U.S. Pat. Appl. Publ., 20 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------|----------|-----------------|----------|
| US 2004209904 | A1 | 20041021 | US 2004-824731 | 20040415 |
| AU 2004230209 | A1 | 20041028 | AU 2004-230209 | 20040408 |
| CA 2522522 | AA | 20041028 | CA 2004-2522522 | 20040408 |
| WO 2004092144 | A2 | 20041028 | WO 2004-EP3779 | 20040408 |
| WO 2004092144 | A3 | 20050324 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1620408 A2 20060201 EP 2004-726448 20040408

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK

BR 2004009580 A 20060418 BR 2004-9580 20040408

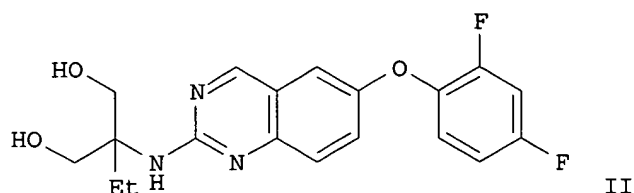
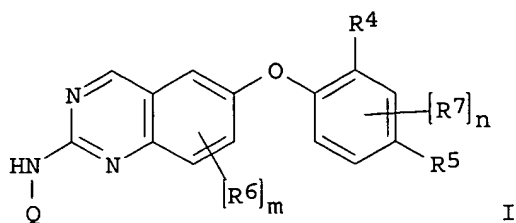
CN 1774425 A 20060517 CN 2004-80010341 20040408

PRIORITY APPLN. INFO.: US 2003-463467P P 20030416

WO 2004-EP3779 W 20040408

OTHER SOURCE(S): MARPAT 141:366245

GI



- AB The title compds. I [R4, R5 = H, halo, CN, haloalkyl, or haloalkoxy (but are not both hydrogen); R6, R7 = alkyl, halo, CN, etc.; Q = a non-aromatic moiety; m = 0-3; n = 0-2] which are useful as p38 kinase inhibitors, were prepared and formulated. E.g., a multi-step synthesis of II, starting from Me 5-chloro-2-nitrobenzoate and 2,4-difluorophenol, which showed IC50 of <0.10 μ M against p38 MAP kinase, was given.
- IC ICM A61K031-517
ICS C07D043-02
- INCL 514266200; X51-426.64; X54-428.4; X54-429.3
- CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63
- ST quinazoline prepn formulation **p38** MAP kinase inhibitor
- IT Inflammation
(Crohn's disease, treating; preparation of substituted quinazolines as **p38** kinase inhibitors)
- IT Intestine, disease
(Crohn's, treating; preparation of substituted quinazolines as **p38** kinase inhibitors)
- IT Respiratory distress syndrome
(adult, treating; preparation of substituted quinazolines as **p38** kinase inhibitors)
- IT Lung, disease
(chronic obstructive pulmonary disease, treating; preparation of substituted quinazolines as **p38** kinase inhibitors)
- IT Heart, disease
(infarction, treating; preparation of substituted quinazolines as **p38** kinase inhibitors)
- IT Anti-Alzheimer's agents
Antiarthritics
Antiasthmatics
Human
(preparation of substituted quinazolines as **p38** kinase inhibitors)
- IT Inflammation
Spinal column, disease
(spondylitis, treating; preparation of substituted quinazolines as **p38** kinase inhibitors)
- IT Brain, disease
(stroke, treating; preparation of substituted quinazolines as **p38** kinase inhibitors)
- IT Alzheimer's disease

Arthritis
Asthma
Sepsis

(treating; preparation of substituted quinazolines as p38 kinase inhibitors)

- IT 165245-96-5, p38 MAP kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of substituted quinazolines as p38 kinase inhibitors)
- IT 778639-17-1P 778639-18-2P 778639-19-3P 778639-20-6P 778639-21-7P
778639-22-8P 778639-23-9P 778639-24-0P 778639-25-1P 778639-26-2P
778639-27-3P 778639-28-4P 778639-29-5P 778639-30-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
(Uses)
(preparation of substituted quinazolines as p38 kinase inhibitors)
- IT 115-70-8, 2-Amino-2-ethyl-1,3-propanediol 367-27-1, 2,4-Difluorophenol
18542-42-2, 2-(Methylsulfonyl)ethylamine 51282-49-6, Methyl
5-chloro-2-nitrobenzoate 402927-97-3, 1-(Methylsulfonyl)piperidin-4-
amine 778639-39-7, 2-Chloro-6-ethoxyquinazoline
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of substituted quinazolines as p38 kinase inhibitors)
- IT 778639-31-9P 778639-32-0P 778639-33-1P 778639-34-2P 778639-35-3P
778639-36-4P 778639-37-5P 778639-38-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(preparation of substituted quinazolines as p38 kinase inhibitors)

L47 ANSWER 10 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:796707 HCAPLUS

DOCUMENT NUMBER: 139:307789

TITLE: Preparation of imidazopyridopyrimidines as inhibitors
of p-38 kinase

INVENTOR(S): Goldstein, David Michael; Hawley, Ronald
Charles; Lui, Alfred Sui-ting; Sjogren, Eric Brian

PATENT ASSIGNEE(S): F. Hoffmann-La Roche Ag, Switz.

SOURCE: PCT Int. Appl., 61 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

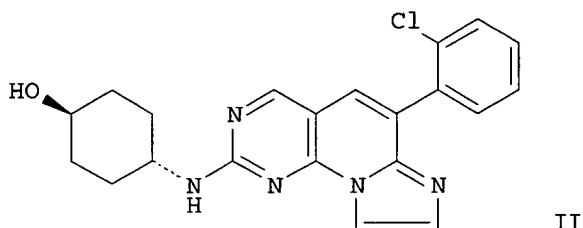
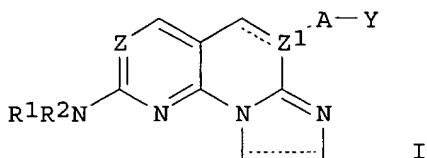
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|--|----------|-----------------|----------|
| WO 2003082871 | A1 | 20031009 | WO 2003-EP3178 | 20030327 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| CA 2479644 | AA | 20031009 | CA 2003-2479644 | 20030327 |
| AU 2003215675 | A1 | 20031013 | AU 2003-215675 | 20030327 |
| BR 2003008937 | A | 20050104 | BR 2003-8937 | 20030327 |
| EP 1492790 | A1 | 20050105 | EP 2003-745276 | 20030327 |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, | | | |

IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
 CN 1646529 A 20050727 CN 2003-807536 20030327
 JP 2006503802 T2 20060202 JP 2003-580336 20030327
 US 2003232847 A1 20031218 US 2003-406364 20030403
 US 6949560 B2 20050927
 US 2005197352 A1 20050908 US 2005-122137 20050504
 PRIORITY APPLN. INFO.: US 2002-369929P P 20020403
 WO 2003-EP3178 W 20030327
 US 2003-406364 A3 20030403
 OTHER SOURCE(S): MARPAT 139:307789
 GI



AB Title compds. I [Z = N, CH; Z1 = N, CH, C; R1 = H, alkyl; R2 = (un)substituted alkyl, aralkyl, cycloalkyl, heterocyclcyl, aryl; A = bond, O, S, s(O), SO2, (un)substituted CH2, NH, CO; Y = alkyl, heterocyclic, (un)substituted cycloalkyl, aryl, heteroaryl] were prepared for use as inhibitors of p-38 kinase. Thus, the title compound II was prepared by treating 4-amino-2-benzylthiopyrimidine-5-carboxaldehyde with 2-ClC6H4CH2CN, cyclizing with ClCH2CHClOEt, oxidizing to the sulfoxide, and reaction with trans-4-aminocyclohexanol. II had IC50 for inhibition of p-38 kinase of 0.01 μ M.

IC ICM C07D471-14
 ICS C07D487-14; A61K031-519; A61P025-00; A61P029-00; A61P011-00; C07D239-00; C07D235-00; C07D221-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
 Section cross-reference(s): 1, 63

ST imidazopyridopyrimidine prepn **p38** kinase inhibitor

IT Inflammation
 (Crohn's disease; preparation of imidazopyridopyrimidines as inhibitors of **p-38** kinase)

IT Intestine, disease
 (Crohn's; preparation of imidazopyridopyrimidines as inhibitors of **p-38** kinase)

IT Respiratory distress syndrome
 (adult; preparation of imidazopyridopyrimidines as inhibitors of **p-38** kinase)

IT Lung, disease
 (chronic obstructive pulmonary disease; preparation of imidazopyridopyrimidines as inhibitors of **p-38** kinase)

IT Intestine, disease
(irritable bowel syndrome; preparation of imidazopyridopyrimidines as inhibitors of p-38 kinase)

IT Alzheimer's disease
Antiarthritics
Arthritis
Human
(preparation of imidazopyridopyrimidines as inhibitors of p-38 kinase)

IT 165245-96-5, p-38 Kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of imidazopyridopyrimidines as inhibitors of p-38 kinase)

IT 610785-97-2P 610785-99-4P 610786-02-2P 610786-03-3P 610786-08-8P
610786-09-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of imidazopyridopyrimidines as inhibitors of p-38 kinase)

IT 124-68-5, 2-Amino-2-methyl-1-propanol 140-75-0, 4-Fluorobenzylamine
371-40-4, 4-Fluoroaniline 623-46-1, 1,2-Dichloro-1-ethoxyethane
1072-72-6, Tetrahydrothiopyran-4-one 2856-63-5, 2-Chlorophenylacetonitrile 3891-07-4, N-(2-Hydroxyethyl)phthalimide
24115-20-6, 4-Fluorophenoxyacetonitrile 27489-62-9, trans-4-Aminocyclohexanol 38041-19-9, Tetrahydropyran-4-amine 49773-20-8,
2-Methylsulfonylethylamine 50541-93-0, 4-Amino-1-benzylpiperidine
335318-13-3 335318-29-1 402740-45-8 610786-18-0 610786-19-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of imidazopyridopyrimidines as inhibitors of p-38 kinase)

IT 6309-59-7P, Tetrahydrothiopyran-4-one oxime 21926-00-1P,
4-Aminotetrahydrothiopyran 182223-53-6P 182223-54-7P 210240-20-3P
402927-96-2P 402927-97-3P 402927-98-4P 402927-99-5P 449809-32-9P
610786-10-2P 610786-11-3P 610786-12-4P 610786-13-5P 610786-15-7P
610786-16-8P 610786-17-9P 610786-20-4P 610786-22-6P 610786-23-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of imidazopyridopyrimidines as inhibitors of p-38 kinase)

IT 610785-98-3P 610786-00-0P 610786-01-1P 610786-04-4P 610786-05-5P
610786-06-6P 610786-07-7P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of imidazopyridopyrimidines as inhibitors of p-38 kinase)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 11 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:719487 HCAPLUS

DOCUMENT NUMBER: 139:246044

TITLE: Bicyclic pyridine and pyrimidine derivatives, e.g., thieno[2,3-d]pyrimidines and analogs, active as p38 kinase inhibitors, and their preparation, pharmaceutical compositions, and uses

INVENTOR(S): Chen, Jian Jeffrey; Dewdney, Nolan James; Stahl, Christoph Martin

PATENT ASSIGNEE(S): F. Hoffman-La Roche Ag, Switz.

SOURCE: PCT Int. Appl., 80 pp.

DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|-------------------|----------|-----------------|-------------|
| WO 2003074530 | A1 | 20030912 | WO 2003-EP2090 | 20030228 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2477721 | AA | 20030912 | CA 2003-2477721 | 20030228 |
| AU 2003210388 | A1 | 20030916 | AU 2003-210388 | 20030228 |
| EP 1485390 | A1 | 20041215 | EP 2003-743361 | 20030228 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| BR 2003008232 | A | 20041228 | BR 2003-8232 | 20030228 |
| CN 1639168 | A | 20050713 | CN 2003-805419 | 20030228 |
| JP 2005526057 | T2 | 20050902 | JP 2003-572998 | 20030228 |
| US 2003207900 | A1 | 20031106 | US 2003-383392 | 20030306 |
| US 2005288312 | A1 | 20051229 | US 2005-202611 | 20050812 |
| US 2006084803 | A1 | 20060420 | US 2005-292217 | 20051130 |
| PRIORITY APPLN. INFO.: | | | US 2002-362373P | P 20020307 |
| | | | US 2002-430508P | P 20021203 |
| | | | WO 2003-EP2090 | W 20030228 |
| | | | US 2003-383392 | A1 20030306 |
| OTHER SOURCE(S): | MARPAT 139:246044 | | | |
| GI | | | | |

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention discloses compds. I, their pharmaceutical formulations, methods of making them, and their uses in the treatment of p38 kinase-mediated diseases [wherein: A is N or CH; R1 is H, alkyl or arylalkyl; R2 is alkyl, hydroxyalkyl, (R'')2NCO-alkylene- (where each R'' is independently H or alkyl), cycloalkyl, heterocyclyl, aryl, heteroaryl, or heteroalkyl; X is O, NR3, or S, wherein R3 is H, alkyl, or aryl; and Y is bond, O, NR', CO, CH(OR'), CH(R'), or S(O)n, wherein n = 0-2; and R' is H or alkyl; and R is aryl or heteroaryl; or an isomer, a pharmaceutically acceptable salt, an ester, or a prodrug thereof]. The compds. are useful for treatment of disorders exacerbated or caused by excessive or unregulated TNF or p38 kinase production. Claimed methods of treatment include uses for treatment of arthritis, Crohn's disease, Alzheimer's disease, irritable bowel syndrome, adult respiratory distress syndrome, and chronic obstructive pulmonary disease. A table of over 40 compds. I is given, and most of these compds. are also claimed individually. The example compds. are mostly thienopyrimidines, but include some furanopyrimidines and pyrrolopyrimidines. For instance, invention compound II (as the HCl salt) was prepared from 4-chloro-2-(methylthio)pyrimidine in 5 steps: (1)

fluorination of chloro using KF and 18-crown-6 in tetraglyme; (2) lithiation in the 5-position with LDA and formylation with EtOCHO; (3) cyclocondensation of the resultant aldehyde with 2'-ClC₆H₄COCH₂SH to form a fused thiophene ring; (4) oxidation of the methylthio group to a Me sulfone using Oxone; and (5) aminolysis of the sulfone with 4-aminotetrahydropyran, followed by chromatog. and acidification in ether. In a test for inhibition of recombinant p38 kinase in vitro, invention compound III gave an IC₅₀ of 104 nM.

- IC ICM C07D495-04
ICS C07D487-04; C07D491-04; A61K031-519; A61P019-02
- CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63
- ST bicyclic pyridine pyrimidine prepn **p38** kinase inhibitor TNF;
thienopyrimidine furanopyrimidine pyrrolopyrimidine prepn treatment
arthritis Crohn Alzheimer ARDS
- IT Inflammation
(Crohn's disease, treatment of; preparation of thienopyrimidines and analogs
as **p38** kinase inhibitors)
- IT Intestine, disease
(Crohn's, treatment of; preparation of thienopyrimidines and analogs as
p38 kinase inhibitors)
- IT Respiratory distress syndrome
(adult, treatment of; preparation of thienopyrimidines and analogs as
p38 kinase inhibitors)
- IT Lung, disease
(chronic obstructive pulmonary disease, treatment of; preparation of
thienopyrimidines and analogs as **p38** kinase inhibitors)
- IT Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors of biosynthesis; preparation of thienopyrimidines and analogs as
p38 kinase inhibitors)
- IT Intestine, disease
(irritable bowel syndrome, treatment of; preparation of thienopyrimidines
and analogs as **p38** kinase inhibitors)
- IT Anti-Alzheimer's agents
Antiarthritics
Human
(preparation of thienopyrimidines and analogs as **p38** kinase
inhibitors)
- IT Alzheimer's disease
Arthritis
(treatment of; preparation of thienopyrimidines and analogs as **p38**
kinase inhibitors)
- IT 598298-05-6P, 2-(Methylsulfinyl)-6-benzylfurano[2,3-d]pyrimidine
RL: BYP (Byproduct); PREP (Preparation)
(byproduct; preparation of thienopyrimidines and analogs as **p38**
kinase inhibitors)
- IT 598297-63-3P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic
preparation); THU (Therapeutic use); BIOL (Biological study); PREP
(Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of thienopyrimidines and analogs as **p38**
kinase inhibitors)
- IT 598297-55-3P 598297-56-4P 598297-57-5P 598297-58-6P 598297-59-7P,
2-[(Tetrahydropyran-4-yl)amino]-6-(2-chlorobenzoyl)thieno[2,3-d]pyrimidine
598297-60-0P 598297-61-1P 598297-62-2P 598297-64-4P 598297-65-5P
598297-66-6P 598297-67-7P 598297-68-8P 598297-69-9P 598297-70-2P
598297-71-3P 598297-72-4P 598297-73-5P 598297-74-6P 598297-75-7P
598297-76-8P 598297-77-9P 598297-78-0P 598297-79-1P 598297-80-4P
598297-81-5P 598297-82-6P, 2-[(Tetrahydropyran-4-yl)amino]-6-

benzylfurano[2,3-d]pyrimidine 598297-83-7P, 2-(Cyclopentylamino)-6-benzylfurano[2,3-d]pyrimidine 598297-84-8P, 2-[(4-Hydroxycyclohexyl)amino]-6-benzylfurano[2,3-d]pyrimidine 598297-85-9P, 2-[(Tetrahydropyran-4-yl)amino]-6-(2-methoxybenzoyl)-7-methylpyrrolo[2,3-d]pyrimidine 598297-86-0P, 2-(Cyclopentylamino)-6-benzyl-7-methylpyrrolo[2,3-d]pyrimidine 598297-87-1P, 2-[(4-Hydroxycyclohexyl)amino]-6-benzyl-7-methylpyrrolo[2,3-d]pyrimidine 598297-88-2P, 2-[(Tetrahydropyran-4-yl)amino]-6-benzyl-7-methylpyrrolo[2,3-d]pyrimidine 598297-89-3P 598297-90-6P 598297-91-7P, 2-(Isopropylamino)-6-benzylfurano[2,3-d]pyrimidine 598297-92-8P, 2-(Phenylamino)-6-(4-methoxyphenyl)-7-phenylpyrrolo[2,3-d]pyrimidine 598297-93-9P, 2-[[1-(2-Hydroxyethyl)-3-hydroxypropyl]amino]-6-(2-methoxybenzoyl)thieno[2,3-d]pyrimidine 598297-94-0P, [6-[(2,4-Difluorophenyl)sulfanyl]thieno[2,3-d]pyrimidin-2-yl](tetrahydropyran-4-yl)amine 598297-95-1P, [6-(2,4-Difluorophenoxy)thieno[2,3-d]pyrimidin-2-yl](tetrahydropyran-4-yl)amine 598297-96-2P, [6-(Phenylsulfanyl)thieno[2,3-d]pyrimidin-2-yl](tetrahydropyran-4-yl)amine 598297-97-3P, 2-[(1,1-Dioxotetrahydro-2H-thiopyran-4-yl)amino]-6-(3-fluorobenzoyl)thieno[2,3-d]pyrimidine 598297-98-4P, 2-[(Tetrahydropyran-4-yl)amino]-6-(2-chlorobenzoyl)thieno[2,3-d]pyrimidine hydrochloride 598297-99-5P
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of thienopyrimidines and analogs as **p38** kinase inhibitors)

IT 165245-96-5, **p-38** MAP kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(inhibitors; preparation of thienopyrimidines and analogs as **p38** kinase inhibitors)

IT 5000-66-8P, 2-Bromo-2'-chloroacetophenone 14080-51-4P 17759-30-7P, 4-(Methylamino)-2-(methylthio)pyrimidine-5-methanol 76360-82-2P, Ethyl 4-(methylamino)-2-(methylthio)pyrimidine-5-carboxylate 117516-97-9P 161124-03-4P, 4-Fluoro-2-(methylthio)pyrimidine 161124-07-8P, 4-Fluoro-2-(methylthio)pyrimidine-5-carboxaldehyde 175657-37-1P, 2-(Acetylthio)-2'-chloroacetophenone 185040-32-8P, 4-(Methylamino)-2-(methylthio)pyrimidine-5-carboxaldehyde 309976-36-1P 595565-59-6P, 2'-Chloro-2-thioacetophenone 598298-00-1P 598298-01-2P, 2-(Methanesulfonyl)-6-(2-chlorobenzoyl)thieno[2,3-d]pyrimidine 598298-02-3P, 2-(Methylthio)-6-(2-methoxybenzoyl)-7-methylpyrrolo[2,3-d]pyrimidine 598298-03-4P 598298-04-5P, 2-(Methylsulfonyl)-6-benzylfurano[2,3-d]pyrimidine 598298-06-7P, 2-(Methylthio)-5-(3-phenylpropyn-1-yl)-6-(methylamino)pyrimidine 598298-07-8P, 2-(Methylthio)-6-benzyl-7-methylpyrrolo[2,3-d]pyrimidine 598298-08-9P, 2-(Methanesulfinyl)-6-benzyl-7-methylpyrrolo[2,3-d]pyrimidine 598298-09-0P, (Tetrahydropyran-4-yl)(thieno[2,3-d]pyrimidin-2-yl)amine 598298-10-3P 598298-11-4P, 4-Chloro-2-(methanesulfonyl)thieno[2,3-d]pyrimidine 598298-12-5P, 2-(Methanesulfonyl)thieno[2,3-d]pyrimidine 598298-13-6P, (6-Iodothieno[2,3-d]pyrimidin-2-yl)(tetrahydropyran-4-yl)amine

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; preparation of thienopyrimidines and analogs as **p38** kinase inhibitors)

IT 107-91-5, Cyanoacetamide 367-27-1, 2,4-Difluorophenol 882-33-7, Phenyl disulfide 1003-03-8, Aminocyclopentane 1996-44-7, 2,4-Difluorobenzenethiol 2142-68-9, 2'-Chloroacetophenone 5909-24-0, Ethyl 4-chloro-2-(methylthio)pyrimidine-5-carboxylate 10147-11-2, 3-Phenyl-1-propyne 31949-21-0, 2'-Methoxy-2-bromoacetophenone 38041-19-9, 4-Aminotetrahydropyran 40018-26-6, 2,5-Dihydroxy-1,4-

dithiane 49844-90-8, 4-Chloro-2-(methylthio)pyrimidine 76510-61-7,
2-(Methylthio)-4-hydroxy-5-iodopyrimidine 111079-19-7,
2-(Methanethio)-4-chloro-5-iodopyrimidine

RL: RCT (Reactant); RACT (Reactant or reagent)

(starting material; preparation of thienopyrimidines and analogs as
p38 kinase inhibitors)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 12 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:202633 HCAPLUS

DOCUMENT NUMBER: 138:238019

TITLE: Preparation of 5-(3-pyridyl)pyrrol-2-amines as
antiinflammatory agents

INVENTOR(S): Goldstein, David Michael; Rotstein, David
Mark

PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.

SOURCE: PCT Int. Appl., 32 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

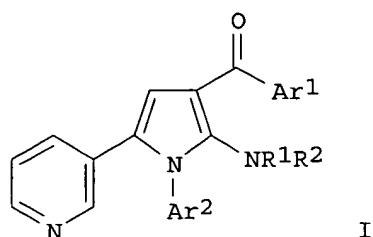
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|--|----------|-----------------|----------|
| WO 2003020715 | A1 | 20030313 | WO 2002-EP9505 | 20020826 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| CA 2458808 | AA | 20030313 | CA 2002-2458808 | 20020826 |
| EP 1423378 | A1 | 20040602 | EP 2002-767427 | 20020826 |
| EP 1423378 | B1 | 20051109 | | |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | |
| BR 2002012077 | A | 20040928 | BR 2002-12077 | 20020826 |
| CN 1547578 | A | 20041117 | CN 2002-816631 | 20020826 |
| JP 2005506324 | T2 | 20050303 | JP 2003-524985 | 20020826 |
| AT 309239 | E | 20051115 | AT 2002-767427 | 20020826 |
| ES 2252509 | T3 | 20060516 | ES 2002-2767427 | 20020826 |
| US 2003130319 | A1 | 20030710 | US 2002-231792 | 20020829 |
| US 6696471 | B2 | 20040224 | | |

PRIORITY APPLN. INFO.: US 2001-316169P P 20010830
WO 2002-EP9505 W 20020826

OTHER SOURCE(S): MARPAT 138:238019
GI



AB The title compds. [I; Ar1, Ar2 = (un)substituted aryl; R1, R2 = H, alkyl, N-protecting group] and their pharmaceutically acceptable salts, useful in the treatment of inflammatory diseases, especially arthritis, were prepared and formulated. Thus, alkylation of benzoylacetonitrile with 3-bromoacetylpyridine.HBr in the presence of NaH in THF followed by reacting 2-benzoyl-4-oxo-4-(pyridin-3-yl)butyronitrile with 4-fluoroaniline in the presence of concentrate HCl afforded I [Ar1 = Ph; Ar2 = 4-FC6H4; R1, R2 = H] which showed IC50 of 1.64x10⁻¹ μM against p-38 MAP kinase.

IC ICM C07D401-04

ICS A61K031-4025; A61P029-00

CC 27-16 (Heterocyclic Compounds (One Hetero Atom))

Section cross-reference(s): 1, 63

ST pyridylpyrroleamine prepn formulation antiinflammatory antiarthritic

p38 MAP kinase; pyrrolamine pyridyl prepn formulation **p38**

MAP kinase inhibitor

IT 165245-96-5, **p38** MAP kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(preparation of 5-(3-pyridyl)pyrrol-2-amines as antiinflammatory agents)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 13 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:738803 HCAPLUS

DOCUMENT NUMBER: 139:307697

TITLE: Design and Synthesis of 4-Azaindoles as Inhibitors of **p38** MAP Kinase

AUTHOR(S): Trejo, Alejandra; Arzeno, Humberto; Browner, Michelle; Chanda, Sushmita; Cheng, Soan; Comer, Daniel D.; Dalrymple, Stacie A.; Dunten, Pete; Lafargue, JoAnn; Lovejoy, Brett; Freire-Moar, Jose; Lim, Julie; McIntosh, Joel; Miller, Jennifer; Papp, Eva; Reuter, Deborah; Roberts, Rick; Sanpablo, Florentino; Saunders, John; Song, Kyung; Villasenor, Armando; Warren, Stephen D.; Welch, Mary; Weller, Paul; Whiteley, Phyllis E.; Zeng, Lu; **Goldstein, David M.**

CORPORATE SOURCE: Department of Medicinal Chemistry, Roche Palo Alto LLC, Palo Alto, CA, 94304, USA

SOURCE: Journal of Medicinal Chemistry (2003), 46(22), 4702-4713

CODEN: JMCMAR; ISSN: 0022-2623

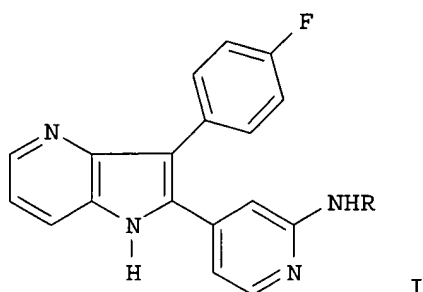
PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 139:307697

GI



- AB Inhibition of the biosynthesis of proinflammatory cytokines such as tumor necrosis factor and interleukin-1 via p38 has been an approach toward the development of a disease modifying agent for the treatment of chronic inflammation and autoimmune diseases. The development of a new core structure of p38 inhibitors, 3-(4-fluorophenyl)-2-(pyridin-4-yl)-1H-pyrrolo[3,2-b]pyridine, is described. X-ray crystallog. data of the lead bound to the active site of p38 was used to guide the optimization of the series. Specific focus was placed on modulating the phys. properties of the core while maintaining potent inhibition of p38. These efforts identified I [R = (R)-2-hydroxypropyl] as a potent inhibitor of p38, which also possessed the required phys. properties worthy of advanced studies.
- CC 28-2 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 27, 75
- ST crystal structure **p38** MAP kinase; azaindole prepn inhibitor
p38 MAP kinase
- IT Crystal structure
Molecular structure
(of **p38** MAP kinase)
- IT Human
(preparation of 4-azaindoles and related compds. as inhibitors of **p38** MAP kinase)
- IT 165245-96-5, **p38** MAP Kinase
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(crystal structure; preparation of 4-azaindoles and related compds. as inhibitors of **p38** MAP kinase)
- IT 34810-03-2, **p38**, biological studies 610270-98-9 610270-99-0
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of 4-azaindoles and related compds. as inhibitors of **p38** MAP kinase)
- IT 610270-90-1P
RL: BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 4-azaindoles and related compds. as inhibitors of **p38** MAP kinase)
- IT 223743-49-5
RL: PAC (Pharmacological activity); BIOL (Biological study)
(preparation of 4-azaindoles and related compds. as inhibitors of **p38** MAP kinase)
- IT 223738-94-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 4-azaindoles and related compds. as inhibitors of **p38** MAP kinase)

IT 223738-90-7P 223738-97-4P 223739-06-8P 223739-61-5P 223739-79-5P
223739-97-7P 223740-56-5P 223740-67-8P 223742-68-5P 610270-66-1P
610270-76-3P 610270-93-4P 610270-94-5P 610270-95-6P 610270-96-7P
610270-97-8P 610271-00-6P 610271-01-7P 610271-02-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL
(Biological study); PREP (Preparation)
(preparation of 4-azaindoles and related compds. as inhibitors of
p38 MAP kinase)

IT 62-53-3, Aniline, reactions 79-08-3 106-40-1, 4-Bromoaniline
106-49-0, 4-Methylaniline, reactions 109-77-3, Malononitrile 371-40-4,
4-Fluoroaniline 459-22-3, 4-Fluorophenylacetoneitrile 540-51-2
872-85-5, 4-Formylpyridine 874-24-8 1120-87-2, 4-Bromopyridine
1194-02-1, 4-Fluorobenzonitrile 2459-09-8 2799-16-8,
(R)-2-Hydroxypropylamine 2799-17-9, (S)-2-Hydroxypropylamine
4595-59-9, 5-Bromopyrimidine 5349-17-7 5470-18-8, 2-Chloro-3-
nitropyridine 6168-72-5, 2-Hydroxy-1-methylethylamine 6298-19-7,
3-Amino-2-chloropyridine 6482-24-2 13325-10-5, 4-Hydroxybutylamine
13552-21-1, 2-Hydroxybutylamine 14254-57-0, Isonicotinoyl chloride
42802-94-8 54035-94-8 56477-57-7 70298-89-4 116332-54-8
130387-74-5, 4-Fluorophenylmagnesium chloride 610271-05-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of 4-azaindoles and related compds. as inhibitors of
p38 MAP kinase)

IT 73406-50-5P, Ethyl 3-hydroxypicolinate 115858-97-4P 115858-98-5P
153254-91-2P 223738-89-4P 223742-77-6P 223742-81-2P 223742-86-7P
223742-89-0P 223742-93-6P 223742-96-9P 223743-15-5P 223743-18-8P
223743-21-3P 223743-23-5P 223743-26-8P 223743-28-0P 223743-30-4P
610270-69-4P 610270-72-9P 610270-74-1P 610270-84-3P 610270-86-5P
610270-88-7P 610270-92-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(preparation of 4-azaindoles and related compds. as inhibitors of
p38 MAP kinase)

IT 610271-03-9P 610271-04-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of 4-azaindoles and related compds. as inhibitors of
p38 MAP kinase)

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 14 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:637680 HCAPLUS
DOCUMENT NUMBER: 137:185502
TITLE: Preparation of 2,6-disubstituted 7-oxopyrido[2,3-
d]pyrimidines for treating p38 mediated
disorders
INVENTOR(S): Chen, Jian Jeffrey; Dunn, James Patrick;
Goldstein, David Michael; Stahl, Christoph
Martin
PATENT ASSIGNEE(S): F. Hoffmann-La Roche Ag, Switz.
SOURCE: PCT Int. Appl., 207 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------|----------|-----------------|----------|
| WO 2002064594 | A2 | 20020822 | WO 2002-EP1106 | 20020204 |

WO 2002064594 A3 20030109

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2434834 AA 20020822 CA 2002-2434834 20020204
EP 1361880 A2 20031119 EP 2002-726103 20020204
EP 1361880 B1 20050928

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

BR 2002007172 A 20040330 BR 2002-7172 20020204

CN 1503672 A 20040609 CN 2002-804834 20020204

JP 2004525896 T2 20040826 JP 2002-564525 20020204

NZ 526961 A 20050324 NZ 2002-526961 20020204

AT 305303 E 20051015 AT 2002-726103 20020204

RU 2269527 C2 20060210 RU 2003-125887 20020204

ES 2249574 T3 20060401 ES 2002-2726103 20020204

US 2003171584 A1 20030911 US 2002-73845 20020211

US 6696566 B2 20040224

ZA 2003005938 A 20041101 ZA 2003-5938 20030731

NO 2003003540 A 20030811 NO 2003-3540 20030811

BG 108085 A 20041230 BG 2003-108085 20030812

US 2004116698 A1 20040617 US 2003-722703 20031125

PRIORITY APPLN. INFO.: US 2001-268375P P 20010212

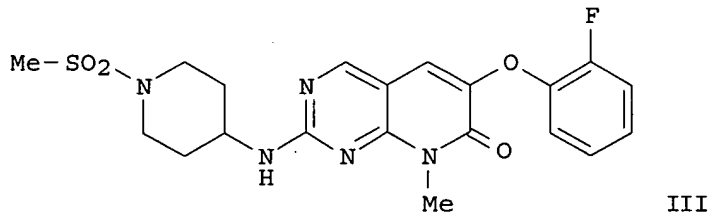
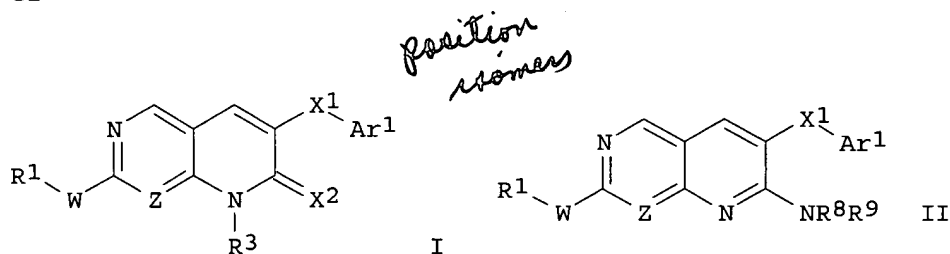
US 2001-334654P P 20011130

WO 2002-EP1106 W 20020204

US 2002-73845 A1 20020211

OTHER SOURCE(S): MARPAT 137:185502

GI



AB The title compds. with general formula I or II [wherein Z = N or CH; W = NR2; X1 = O, NR4, S, CR5R6, or CO; R4, R5, and R6 = independently H or alkyl; X2 = O or NR7; Ar1 = (hetero)aryl; R2 = H, alkyl, acyl, alkoxy, carbonyl, aryloxy, carbonyl, heteroalkyl(oxy)carbonyl, or R21-R22; R21 = alkylene or CO; R22 = alkyl or alkoxy; R1 = H, (halo)alkyl,

(hetero)aryl, (hetero)aralkyl, cyclo(alkyl)alkyl, hetero(cyclyl)alkyl, cyanoalkyl, heterocyclyl, or substituted hetero(alkyl)cycloalkyl, heterocycloamino, or acyl(alkylene); R3 = H, (cyclo)alkyl, cycloalkylalkyl, aryl, aralkyl, haloalkyl, heteroalkyl, cyanoalkyl, acylalkylene, (un)substituted amino; R7 = H or alkyl; R8 and R9 = independently H, (cyclo)alkyl, aryl(sulfonyl), aralkyl, cycloalkylalkyl, heteroalkyl, alkylsulfonyl, acyl, etc.; and pharmaceutically acceptable salts thereof] were prepared. For example, the substitution reaction of 6-(2-fluorophenoxy)-8-methyl-2-(methylsulfonyl)pyrido[2,3-d]pyrimidin-7(8H)-one (preparation given) and 1-(methylsulfonyl)piperidin-4-amine

(preparation

given), followed by salt formation, gave the phenoxypyrido[2,3-d]pyrimidinone III•HCl. I and II have IC50 activity against p38 kinase in the range of 0.1-5000 nM, with the majority being 1-1000 nM. I and II are useful for the treatment of arthritis, Crohn's disease, irritable bowel syndrome, adult respiratory distress syndrome, chronic obstructive pulmonary disease, or Alzheimer's disease (no data).

IC ICM C07D487-04

ICS C07D471-04; C07D519-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

ST pyridopyrimidine pyridopyrimidinone oxopyridopyrimidine prepn treatment p38 disorder; pyridopyrimidinone pyridopyrimidine oxopyridopyrimidine prepn Alzheimer disease treatment

IT Inflammation

(Crohn's disease; preparation of oxopyrido[2,3-d]pyrimidines for treating p38 mediated disorders)

IT Intestine, disease

(Crohn's; preparation of oxopyrido[2,3-d]pyrimidines for treating p38 mediated disorders)

IT Respiratory distress syndrome

(adult; preparation of oxopyrido[2,3-d]pyrimidines for treating p38 mediated disorders)

IT Lung, disease

(chronic obstructive pulmonary disease; preparation of oxopyrido[2,3-d]pyrimidines for treating p38 mediated disorders)

IT Intestine, disease

(irritable bowel syndrome; preparation of oxopyrido[2,3-d]pyrimidines for treating p38 mediated disorders)

IT Alzheimer's disease

Anti-Alzheimer's agents

Antiarthritics

Arthritis

Human

(preparation of oxopyrido[2,3-d]pyrimidines for treating p38 mediated disorders)

IT 449808-64-4P 449809-00-1P 449809-02-3P 449809-18-1P 449809-33-0P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(inhibitor; preparation of oxopyrido[2,3-d]pyrimidines for treating p38 mediated disorders)

IT 449808-60-0P 449808-61-1P 449808-63-3P 449808-65-5P 449808-66-6P
 449808-67-7P 449808-68-8P 449808-69-9P 449808-70-2P 449808-71-3P
 449808-73-5P 449808-74-6P 449808-75-7P 449808-76-8P 449808-77-9P
 449808-78-0P 449808-79-1P 449808-80-4P 449808-81-5P 449808-83-7P
 449808-84-8P 449808-85-9P 449808-86-0P 449808-87-1P 449808-88-2P
 449808-89-3P 449808-90-6P 449808-91-7P 449808-93-9P 449808-94-0P
 449808-95-1P 449808-96-2P 449808-97-3P 449808-98-4P 449809-01-2P
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|--------------|--------------|--------------|--------------|--------------|
| 449809-10-3P | 449809-11-4P | 449809-12-5P | 449809-13-6P | 449809-15-8P |
| 449809-16-9P | 449809-17-0P | 449809-19-2P | 449809-20-5P | 449809-21-6P |
| 449809-23-8P | 449809-24-9P | 449809-25-0P | 449809-26-1P | 449809-27-2P |
| 449809-28-3P | 449809-29-4P | 449809-31-8P | 449809-32-9P | 449809-34-1P |
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| 449809-46-5P | 449809-47-6P | 449809-48-7P | 449809-49-8P | 449809-51-2P |
| 449809-52-3P | 449809-53-4P | 449809-54-5P | 449809-55-6P | 449809-56-7P |
| 449809-57-8P | 449809-58-9P | 449809-59-0P | 449809-60-3P | 449809-61-4P |
| 449809-62-5P | 449809-63-6P | 449809-64-7P | 449809-65-8P | 449809-66-9P |
| 449809-67-0P | 449809-68-1P | 449809-70-5P | 449809-71-6P | 449809-72-7P |
| 449809-73-8P | 449809-74-9P | 449809-75-0P | 449809-76-1P | 449809-77-2P |
| 449809-78-3P | 449809-79-4P | 449809-80-7P | 449809-81-8P | 449809-82-9P |
| 449809-83-0P | 449809-84-1P | 449809-85-2P | 449809-86-3P | 449809-87-4P |
| 449809-88-5P | 449809-89-6P | 449809-90-9P | 449809-91-0P | 449809-92-1P |
| 449809-93-2P | 449809-94-3P | 449809-95-4P | 449809-96-5P | 449809-97-6P |
| 449809-98-7P | 449809-99-8P | 449810-00-8P | 449810-01-9P | 449810-02-0P |
| 449810-03-1P | 449810-04-2P | 449810-05-3P | 449810-06-4P | 449810-07-5P |
| 449810-08-6P | 449810-09-7P | 449810-10-0P | 449810-11-1P | 449810-12-2P |
| 449810-13-3P | 449810-14-4P | 449810-15-5P | 449810-16-6P | 449810-17-7P |
| 449810-18-8P | 449810-19-9P | 449810-20-2P | 449810-21-3P | 449810-22-4P |
| 449810-23-5P | 449810-24-6P | 449810-25-7P | 449810-26-8P | 449810-27-9P |
| 449810-28-0P | 449810-29-1P | 449810-30-4P | 449810-31-5P | 449810-32-6P |
| 449810-33-7P | 449810-34-8P | 449810-35-9P | 449810-36-0P | 449810-37-1P |
| 449810-38-2P | 449810-39-3P | 449810-40-6P | 449810-41-7P | 449810-42-8P |
| 449810-43-9P | 449810-44-0P | 449810-45-1P | 449810-46-2P | 449810-47-3P |
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| 449810-55-3P | 449810-57-5P | 449810-59-7P | 449810-61-1P | 449810-63-3P |
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| 449810-74-6P | 449810-76-8P | 449810-78-0P | 449810-84-8P | 449810-88-2P |
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| 449810-98-4P | 449810-99-5P | 449811-00-1P | 449811-01-2P | 449811-02-3P |
| 449811-04-5P | 449811-05-6P | 449811-06-7P | 449811-92-1P | 449811-94-3P |
| 449811-95-4P | 449811-96-5P | | | |

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(inhibitor; preparation of oxopyrido[2,3-d]pyrimidines for treating p38 mediated disorders)

| | | | | |
|---------------|--------------|--------------|--------------|--------------|
| IT 6309-59-7P | 17277-58-6P | 17759-30-7P | 17918-67-1P | 21926-00-1P |
| 24115-20-6P | 39856-89-8P | 70772-78-0P | 76360-82-2P | 100193-64-4P |
| 105161-35-1P | 112434-18-1P | 168297-76-5P | 182223-53-6P | 182223-54-7P |
| 185040-32-8P | 185040-33-9P | 185040-34-0P | 185040-35-1P | 335318-29-1P |
| 402927-96-2P | 402927-97-3P | 449808-45-1P | 449808-46-2P | 449808-47-3P |
| 449808-48-4P | 449808-49-5P | 449808-50-8P | 449808-51-9P | 449808-53-1P |
| 449808-54-2P | 449808-55-3P | 449808-56-4P | 449808-57-5P | 449808-58-6P |
| 449808-59-7P | 449811-08-9P | 449811-09-0P | 449811-10-3P | 449811-11-4P |
| 449811-12-5P | 449811-13-6P | 449811-14-7P | 449811-16-9P | 449811-17-0P |
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| 449811-26-1P | 449811-27-2P | 449811-28-3P | 449811-29-4P | 449811-30-7P |
| 449811-31-8P | 449811-32-9P | 449811-34-1P | 449811-35-2P | 449811-36-3P |
| 449811-37-4P | 449811-38-5P | 449811-39-6P | 449811-40-9P | 449811-42-1P |
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| 449811-49-8P | 449811-50-1P | 449811-51-2P | 449811-53-4P | 449811-54-5P |
| 449811-56-7P | 449811-57-8P | 449811-58-9P | 449811-59-0P | 449811-60-3P |
| 449811-89-6P | 449811-90-9P | 449811-91-0P | | |

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; preparation of oxopyrido[2,3-d]pyrimidines for treating

p38 mediated disorders)

IT 165245-96-5, **p38 Kinase**
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (preparation of oxopyrido[2,3-d]pyrimidines for treating **p38**
 mediated disorders)

IT 770-31-0P
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (preparation of oxopyrido[2,3-d]pyrimidines for treating **p38**
 mediated disorders)

IT 62-53-3, Aniline, reactions 64-04-0, Phenethylamine 75-30-9,
 2-Iodopropane 78-81-9, Isobutylamine 78-84-2, Isobutyraldehyde
 96-32-2, Methyl bromoacetate 98-09-9, Benzenesulfonyl chloride
 100-46-9, Benzylamine, reactions 104-10-9, 2-(4-Aminophenyl)ethanol
 108-98-5, Thiophenol, reactions 109-55-7, N,N-Dimethylpropane-1,3-
 diamine 109-73-9, Butylamine, reactions 109-85-3, 2-Methoxyethylamine
 123-42-2, 4-Hydroxy-4-methyl-2-pentanone 124-68-5, 2-Amino-2-methylpropan-
 1-ol 367-12-4, 2-Fluorophenol 367-25-9, 2,4-Difluoroaniline
 371-40-4, 4-Fluoroaniline 371-41-5, 4-Fluorophenol 501-53-1, Benzyl
 chloroformate 502-83-0, 2-Amino-4-(methylthio)butan-1-ol 616-30-8,
 3-Aminopropane-1,2-diol 765-30-0, Cyclopropylamine 1001-53-2,
 N-(2-Aminoethyl)acetamide 1003-03-8, Cyclopentylamine 1072-72-6,
 Tetrahydrothiopyran-4-one 1609-86-5, tert-Butyl isocyanate 1939-99-7,
 α -Toluenesulfonyl chloride 2026-48-4 2032-34-0,
 3,3-Diethoxypropanenitrile 2065-23-8, Methyl phenoxyacetate 2454-96-8,
 2-Amino-5-Methylpyridine hydrochloride 2516-47-4, Cyclopropylmethylamine
 2941-20-0, α -Ethylbenzylamine 3218-02-8, Cyclohexanemethanamine
 3731-51-9, Pyridin-2-ylmethylamine 3731-53-1, 4-(Aminomethyl)pyridine
 4244-84-2, Ethyl β -alaninate hydrochloride 4313-56-8 4543-47-9,
 3-Furfurylamine 4572-03-6, 1-(3-Aminopropyl)-4-methylpiperazine
 4841-22-9, Methyl 4-chlorophenoxyacetate 5332-73-0, 3-Methoxypropylamine
 5909-24-0, Ethyl 4-chloro-2-methylthiopyrimidine-5-carboxylate 6126-22-3
 6956-85-0, Methyl 2-chlorophenoxyacetate 7116-38-3 7149-62-4
 7663-77-6, 1-(3-Aminopropyl)pyrrolidin-2-one 10316-79-7 16369-14-5,
 2-Aminopentan-1-ol 16867-03-1, 2-Aminopyridin-3-ol 18944-77-9
 20173-24-4, 2-(Pyridin-3-yl)ethylamine 27489-62-9, trans-4-
 Aminocyclohexanol 27578-60-5, 2-Piperidin-1-ylethylamine 28875-17-4,
 N-(tert-Butoxycarbonyl)-L-alanine methyl ester 38041-19-9,
 4-Aminotetrahydropyran 38519-63-0, 4-(2-Diethylaminoethoxy)aniline
 40296-46-6 50541-93-0, 4-Amino-1-benzylpiperidine 58859-46-4, Ethyl
 4-amino-1-piperidinecarboxylate 70183-89-0 129368-01-0 138564-16-6
 141286-91-1, Methyl 2,6-difluorophenoxyacetate 210240-73-6 215940-92-4
 226396-70-9 449811-63-6 449811-69-2 449811-71-6 449811-73-8
 449811-75-0 449811-76-1 449811-78-3 449811-79-4 449811-81-8
 449811-82-9 449811-84-1 449811-85-2 449811-86-3 449811-87-4
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (reactant; preparation of oxopyrido[2,3-d]pyrimidines for treating
p38 mediated disorders)

L47 ANSWER 15 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:171896 HCAPLUS

DOCUMENT NUMBER: 136:232316

TITLE: 7-Oxopyridopyrimidines as inhibitors of cellular
 proliferation, and particularly as inhibitors of
p38 kinase, for treatment of **p38**
 -related conditions

INVENTOR(S): Chen, Jian Jeffrey; Dunn, James Patrick;
Goldstein, David Michael; Lim, Julie Anne

PATENT ASSIGNEE(S): F. Hoffmann-La Roche Ag, Switz.

SOURCE: PCT Int. Appl., 135 pp.

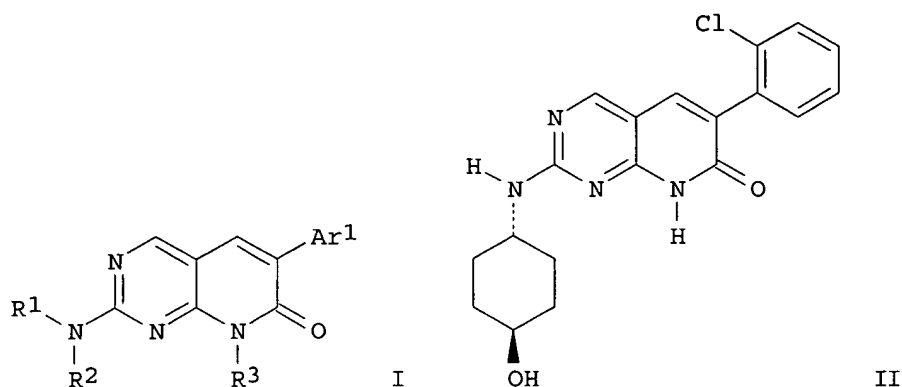
CODEN: PIXXD2

DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|-------------|
| WO 2002018380 | A1 | 20020307 | WO 2001-EP9689 | 20010822 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2420286 | AA | 20020307 | CA 2001-2420286 | 20010822 |
| AU 2001093784 | A5 | 20020313 | AU 2001-93784 | 20010822 |
| EP 1315726 | A1 | 20030604 | EP 2001-974206 | 20010822 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| BR 2001013628 | A | 20030701 | BR 2001-13628 | 20010822 |
| JP 2004507541 | T2 | 20040311 | JP 2002-523895 | 20010822 |
| US 2002055513 | A1 | 20020509 | US 2001-943338 | 20010830 |
| US 6518276 | B2 | 20030211 | | |
| US 2002137756 | A1 | 20020926 | US 2001-943407 | 20010830 |
| US 6506749 | B2 | 20030114 | | |
| US 2003153586 | A1 | 20030814 | US 2002-230723 | 20020829 |
| US 6861423 | B2 | 20050301 | | |
| US 2003144307 | A1 | 20030731 | US 2002-315633 | 20021210 |
| US 6753427 | B2 | 20040622 | | |
| ZA 2003001079 | A | 20040507 | ZA 2003-1079 | 20030207 |
| US 2004192709 | A1 | 20040930 | US 2004-816554 | 20040401 |
| PRIORITY APPLN. INFO.: | | | | |
| | | | US 2000-229584P | P 20000831 |
| | | | US 2000-229577P | P 20000831 |
| | | | WO 2001-EP9689 | W 20010822 |
| | | | US 2001-943338 | A3 20010830 |
| | | | US 2001-943407 | A1 20010830 |
| | | | US 2002-315633 | A3 20021210 |

position names

OTHER SOURCE(S): MARPAT 136:232316
 GI



- AB Compds. I are disclosed [wherein: R₁ = H or alkyl; R₂ = substituted cycloalkyl, hetero-substituted cycloalkyl, heteroalkyl-substituted cycloalkyl, hetero-substituted cycloalkyl-aryl, heterocyclyl, heterocyclylspirocycloalkyl, aralkoxy, alkoxy, -alkylene-S(O)_n-alkyl (where n = 1 or 2) or SO₂Ar₂; R₃ = H, amino, monoalkylamino, dialkylamino, acylamino, NRaC(:O)Rb (where Ra = H or alkyl, and Rb = heterocyclyl or heteroalkyl), alkyl, cycloalkyl, aryl, aralkyl, haloalkyl, heteroalkyl, cyanoalkyl, -alkylene-C(O)R (where R = H, alkyl, OH, alkoxy, amino, monoalkylamino or dialkylamino), acyl, or phthalimidoalkyl; and each of Ar₁ and Ar₂ = aryl]. Also disclosed in claims is their use for treatment of disorders selected from the group consisting of arthritis, Crohn's disease, Alzheimer's disease, irritable bowel syndrome, adult respiratory distress syndrome, and chronic obstructive pulmonary disease. A list of 151 compds. I is given, as well as approx. 100 synthetic examples. For instance, cyclocondensation of 4-amino-2-(methylthio)pyrimidine-5-carboxaldehyde with Et (2-chlorophenyl)acetate, followed by oxidation of the sulfide to a sulfone with Oxone, and displacement of the Me sulfone with trans-4-aminocyclohexanol, gave 78% title compound II. In an in vitro p38 assay, I had IC₅₀ values ranging from about 4.76 μM to about 0.0003 μM.
- IC ICM C07D471-04
ICS A61K031-519; A61P031-00; A61P029-00; C07D471-04; C07D239-00; C07D221-00
- CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
- ST oxopyridopyrimidine prepn **p38** kinase inhibitor; pyridopyrimidine prepn inhibitor cellular proliferation
- IT Inflammation
(Crohn's disease, treatment; preparation of oxopyridopyrimidines as **p38** kinase inhibitors)
- IT Intestine, disease
(Crohn's, treatment; preparation of oxopyridopyrimidines as **p38** kinase inhibitors)
- IT Respiratory distress syndrome
(adult, treatment; preparation of oxopyridopyrimidines as **p38** kinase inhibitors)
- IT Lung, disease
(chronic obstructive pulmonary disease, treatment; preparation of oxopyridopyrimidines as **p38** kinase inhibitors)
- IT Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors of production; preparation of oxopyridopyrimidines as **p38**)

kinase inhibitors)

IT Intestine, disease
(irritable bowel syndrome, treatment; preparation of oxopyridopyrimidines as p38 kinase inhibitors)

IT Anti-Alzheimer's agents
Antiarthritics
Cytotoxic agents
(preparation of oxopyridopyrimidines as p38 kinase inhibitors)

IT 402928-12-5P
RL: BYP (Byproduct); PREP (Preparation)
(byproduct; preparation of oxopyridopyrimidines as p38 kinase inhibitors)

IT 402927-35-9P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of oxopyridopyrimidines as p38 kinase inhibitors)

| | | | | | |
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| | 402925-81-9P | 402925-83-1P | 402925-84-2P | 402925-85-3P | 402925-86-4P |
| | 402925-87-5P | 402925-88-6P | 402925-89-7P | 402925-90-0P | 402925-91-1P |
| | 402925-92-2P | 402925-93-3P | 402925-94-4P | 402925-95-5P | 402925-96-6P |
| | 402925-98-8P | 402925-99-9P | 402926-00-5P | 402926-01-6P | 402926-02-7P |
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| | 402926-64-1P | 402926-65-2P | 402926-66-3P | 402926-67-4P | 402926-68-5P |
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| | 402926-74-3P | 402926-75-4P | 402926-76-5P | 402926-77-6P | 402926-79-8P |
| | 402926-80-1P | 402926-81-2P | 402926-82-3P | 402926-83-4P | 402926-84-5P |
| | 402926-85-6P | 402926-86-7P | 402926-87-8P | 402926-88-9P | 402926-89-0P |
| | 402926-90-3P | 402926-91-4P | 402926-92-5P | 402926-93-6P | 402926-95-8P |
| | 402926-96-9P | 402926-98-1P | 402927-00-8P | 402927-01-9P | 402927-03-1P |
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| | 402927-24-6P | 402927-25-7P | 402927-26-8P | 402927-27-9P | 402927-28-0P |
| | 402927-29-1P | 402927-30-4P | 402927-31-5P | 402927-32-6P | 402927-33-7P |
| | 402927-34-8P | 402927-36-0P | 402927-37-1P | 402927-38-2P | 402927-39-3P |
| | 402927-40-6P | 402927-41-7P | 402927-42-8P | 402927-43-9P | 402927-44-0P |
| | 402927-45-1P | 402927-46-2P | 402927-47-3P | 402927-48-4P | 402927-49-5P |
| | 402927-50-8P | 402927-51-9P | 402927-52-0P | 402927-53-1P | 402927-54-2P |
| | 402927-55-3P | 402927-56-4P | 402927-57-5P | 402927-58-6P | 402927-59-7P |
| | 402927-60-0P | 402927-61-1P | 402927-62-2P | 402927-63-3P | |

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of oxopyridopyrimidines as p38 kinase inhibitors)

inhibitors)

IT 383-50-6P, 2-Fluoroethyl tosylate 588-36-3P, 4-Amino-2-(methylthio)pyrimidine-5-methanol 770-31-0P, 4-Amino-2-(methylthio)pyrimidine-5-carboxaldehyde 776-53-4P, Ethyl 4-amino-2-(methylthio)pyrimidine-5-carboxylate 2251-06-1P, Ethyl 4-[(4-fluorophenyl)amino]-2-(methylthio)pyrimidine-5-carboxylate 6309-59-7P, Tetrahydrothiopyran-4-one oxime 17759-30-7P, 4-(Methylamino)-2-(methylthio)pyrimidine-5-methanol 21926-00-1P, 4-Aminotetrahydrothiopyran 61224-82-6P, 4-(Ethylsulfanyl)butan-2-one 76360-82-2P, Ethyl 4-(methylamino)-2-(methylthio)pyrimidine-5-carboxylate 97181-50-5P, 4-(Trifluoroacetamido)-1-benzylpiperidine 97181-51-6P, 4-(Trifluoroacetamido)piperidine 102669-01-2P 105161-35-1P, 4-Amino-2-sulfanylpiperidine-5-carboxaldehyde 119712-80-0P, 4-(Ethylsulfanyl)butan-2-one oxime 161124-03-4P, 4-Fluoro-2-(methylthio)pyrimidine 182223-53-6P, Benzyl (1-benzylpiperidin-4-yl)carbamate 182223-54-7P, Benzyl piperidin-4-ylcarbamate 185040-32-8P, 4-(Methylamino)-2-(methylthio)pyrimidine-5-carboxaldehyde 187217-99-8P, 4-Amino-1-(2,2,2-trifluoroethyl)piperidine 210240-20-3P 211247-46-0P, 4-(Cyclopropylamino)-5-formyl-2-(methylthio)pyrimidine 335653-59-3P, 4-(N-BOC-amino)-1-(2,2,2-trifluoroethyl)piperidine 402740-25-4P 402740-26-5P, 6-(2-Chlorophenyl)-2-(methanesulfonyl)pyrido[2,3-d]pyrimidin-7-ol 402740-43-6P 402740-45-8P, 6-(2-Chlorophenyl)-2-(methylthio)pyrido[2,3-d]pyrimidin-7-ol 402740-85-6P 402927-64-4P 402927-65-5P 402927-66-6P 402927-67-7P 402927-68-8P 402927-69-9P 402927-70-2P 402927-71-3P 402927-72-4P 402927-73-5P 402927-74-6P 402927-75-7P, N-(2-Cyanoethyl)-4-aminopiperidine 402927-76-8P 402927-77-9P 402927-78-0P 402927-79-1P 402927-80-4P 402927-81-5P 402927-82-6P 402927-83-7P 402927-84-8P 402927-85-9P 402927-86-0P 402927-87-1P 402927-88-2P 402927-89-3P 402927-90-6P, 4-[(4-Fluorophenyl)amino]-2-(methylthio)pyrimidine-5-methanol 402927-91-7P, 4-[(4-Fluorophenyl)amino]-2-(methylthio)pyrimidine-5-carboxaldehyde 402927-92-8P 402927-93-9P 402927-94-0P 402927-95-1P 402927-96-2P, Benzyl [1-(methylsulfonyl)piperidin-4-yl]carbamate 402927-97-3P, 1-(Methylsulfonyl)piperidin-4-amine 402927-98-4P 402927-99-5P 402928-00-1P 402928-01-2P 402928-02-3P 402928-03-4P 402928-04-5P 402928-05-6P 402928-06-7P 402928-07-8P 402928-08-9P 402928-09-0P, 2-Amino-4-(ethylsulfanyl)butane

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; preparation of oxypyridopyrimidines as p38 kinase inhibitors)

IT 75-08-1, Ethanethiol 78-84-2, Isobutyraldehyde 78-94-4, Methyl vinyl ketone, reactions 96-30-0, 2-Chloro-N-methylacetamide 96-32-2, Methyl bromoacetate 98-59-9, p-Toluenesulfonyl chloride 100-39-0, Benzyl bromide 107-13-1, Acrylonitrile, reactions 115-77-5, 1,1,1-Tris(hydroxymethyl)ethanol, reactions 371-40-4, 4-Fluoroaniline 371-62-0, 2-Fluoroethanol 501-53-1, Benzyl chloroformate 504-63-2, 1,3-Propanediol 558-30-5, Isobutylene oxide 765-30-0, Cyclopropylamine 1072-72-6, Tetrahydrothiopyran-4-one 1129-26-6, 4-Methoxybenzenesulfonamide 2032-34-0, 3,3-Diethoxypropanenitrile 2615-25-0, trans-1,4-Diaminocyclohexane 2675-89-0, 2-Chloro-N,N-dimethylacetamide 3680-02-2, Methyl vinyl sulfone 3891-07-4, N-(2-Hydroxyethyl)phthalimide 4313-56-8 4319-49-7, 4-Aminomorpholine 4704-94-3, 2-(Hydroxymethyl)-1,3-propanediol 5909-24-0, Ethyl 4-chloro-2-(methylthio)pyrimidine-5-carboxylate 6338-70-1, Tetrahydro-3-thiopheneamine 1,1-dioxide 10316-79-7, (1-(Hydroxymethyl)cyclopentyl)amine 15159-40-7, 4-Morpholinecarbonyl chloride 15827-56-2, cis-1,4-Diaminocyclohexane 27489-62-9, trans-4-Aminocyclohexanol 36768-62-4, 4-Amino-2,2,6,6-

tetramethylpiperidine 38041-19-9, 4-Aminotetrahydropyran 40061-54-9,
 Ethyl (2-chlorophenyl)acetate 40525-78-8, cis-4-Aminocyclohexanol
 49844-90-8, 4-Chloro-2-(methylthio)pyrimidine 50541-93-0,
 4-Amino-1-benzylpiperidine 51498-33-0, Ethyl 4-
 aminocyclohexanecarboxylate 58859-46-4, Ethyl 4-aminopiperidine-1-
 carboxylate 73874-95-0 76513-69-4, 2-(Trimethylsilyl)ethoxymethyl
 chloride 89854-94-4 93550-77-7, (2-Iodoethoxy)triisopropylsilane
 97096-16-7, (1,4-Dioxaspiro[4.5]dec-8-yl)amine 99724-19-3 111705-51-2,
 (S)-3-(N-Tritylamino)tetrahydrofuran 164646-07-5, 4-
 (Aminomethyl)cyclohexanol 402928-10-3 402928-11-4
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (precursor; preparation of oxopyridopyrimidines as p38 kinase
 inhibitors)

IT 165245-96-5, p-38 Kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (preparation of oxopyridopyrimidines as p38 kinase inhibitors)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 16 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:171895 HCAPLUS

DOCUMENT NUMBER: 136:216763

TITLE: Preparation of 7-oxopyridopyrimidines as p38
 MAP kinase inhibitors

INVENTOR(S): Arzeno, Humberto Bartolome; Chen, Jian Jeffrey; Dunn,
 James Patrick; Goldstein, David Michael;
 Lim, Julie Anne

PATENT ASSIGNEE(S): F. Hoffmann-La Roche Ag, Switz.

SOURCE: PCT Int. Appl., 64 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

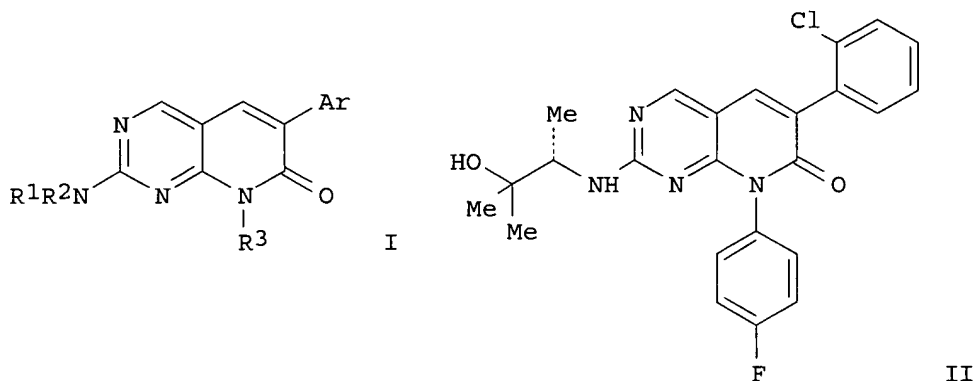
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|--|----------|------------------|----------|
| WO 2002018379 | A2 | 20020307 | WO 2001-EP9688 | 20010822 |
| WO 2002018379 | A3 | 20020725 | | |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| CA 2420122 | AA | 20020307 | CA 2001-2420122 | 20010822 |
| AU 2002012147 | A5 | 20020313 | AU 2002-12147 | 20010822 |
| EP 1315727 | A2 | 20030604 | EP 2001-980258 | 20010822 |
| EP 1315727 | B1 | 20050629 | | |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | |
| BR 2001013590 | A | 20030722 | BR 2001-13590 | 20010822 |
| JP 2004507540 | T2 | 20040311 | JP 2002-523894 | 20010822 |
| AT 298751 | E | 20050715 | AT 2001-980258 | 20010822 |
| ES 2243568 | T3 | 20051201 | ES 2001-1980258 | 20010822 |
| CN 1721412 | A | 20060118 | CN 2005-10083529 | 20010822 |
| US 2002055513 | A1 | 20020509 | US 2001-943338 | 20010830 |

| | | | | |
|------------------------|----|----------|-----------------|-------------|
| US 6518276 | B2 | 20030211 | | |
| US 2003153586 | A1 | 20030814 | US 2002-230723 | 20020829 |
| US 6861423 | B2 | 20050301 | | |
| US 2003144307 | A1 | 20030731 | US 2002-315633 | 20021210 |
| US 6753427 | B2 | 20040622 | | |
| ZA 2003001078 | A | 20040507 | ZA 2003-1078 | 20030207 |
| US 2004192709 | A1 | 20040930 | US 2004-816554 | 20040401 |
| PRIORITY APPLN. INFO.: | | | US 2000-229577P | P 20000831 |
| | | | US 2000-229584P | P 20000831 |
| | | | CN 2001-815027 | A3 20010822 |
| | | | WO 2001-EP9688 | W 20010822 |
| | | | US 2001-943338 | A3 20010830 |
| | | | US 2001-943407 | A1 20010830 |
| | | | US 2002-315633 | A3 20021210 |

OTHER SOURCE(S) : MARPAT 136:216763
GI



AB The present invention provides compds. of the formula I [R₁ = H, alkyl; R₂ = alkoxy-substituted alkyl, heterocyclyl, cycloalkyl; etc.; R₁R₂ = heterocyclyl; R₃ = H, alkyl, amino, aryl, acyl, etc.; Ar = aryl], a prodrug or a pharmaceutically acceptable salt thereof, and processes for their preparation and their use for the treatment of p38 mediated disorders. Thus, II was prepared and inhibited p38 MAP kinase in vitro with IC₅₀ of 0.0003 μM.

IC ICM C07D471-04

ICS A61K031-519; A61P025-00; C07D239-46; C07D471-04; C07D239-00; C07D221-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

ST oxopyridopyrimidine prepn **p38** MAP kinase inhibitor;
pyridopyrimidine oxo prepn **p38** MAP kinase inhibitor

IT Inflammation
(Crohn's disease, treatment; preparation of 7-oxopyridopyrimidines as **p38** MAP kinase inhibitors)

IT Intestine, disease
(Crohn's, treatment; preparation of 7-oxopyridopyrimidines as **p38** MAP kinase inhibitors)

IT Respiratory distress syndrome
(adult, treatment; preparation of 7-oxopyridopyrimidines as **p38** MAP kinase inhibitors)

IT Lung, disease
(chronic obstructive pulmonary disease, treatment; preparation of

7-oxopyridopyrimidines as p38 MAP kinase inhibitors)

IT Intestine, disease
(irritable bowel syndrome, treatment; preparation of 7-oxopyridopyrimidines as p38 MAP kinase inhibitors)

IT Anti-Alzheimer's agents
Antiarthritics
Human
(preparation of 7-oxopyridopyrimidines as p38 MAP kinase inhibitors)

IT 165245-96-5, p38 MAP kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of 7-oxopyridopyrimidines as p38 MAP kinase inhibitors)

IT 402740-27-6P 402740-28-7P 402740-29-8P 402740-30-1P 402740-31-2P
402740-32-3P 402740-33-4P 402740-34-5P 402740-35-6P 402740-36-7P
402740-37-8P 402740-38-9P 402740-39-0P 402740-40-3P 402740-41-4P
402740-42-5P 402740-56-1P 402740-57-2P 402740-58-3P 402740-59-4P
402740-60-7P 402740-61-8P 402740-62-9P 402740-63-0P 402740-64-1P
402740-65-2P 402740-66-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 7-oxopyridopyrimidines as p38 MAP kinase inhibitors)

IT 115-69-5 115-70-8 534-03-2, Serinol 683-57-8, 2-Bromoacetamide
2026-48-4 2032-34-0 2675-89-0, 2-Chloro-N,N-dimethylacetamide
2749-11-3 5292-43-3, tert-Butyl bromoacetate 5856-62-2 5909-24-0
7149-42-0 24629-25-2, (S)-Isoleucinol 40061-54-9, Ethyl
(2-chlorophenyl)acetate 53448-09-2, (R)-Leucinol 74608-26-7
112245-13-3, (S)-tert-Leucinol 132431-09-5 402740-85-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of 7-oxopyridopyrimidines as p38 MAP kinase inhibitors)

IT 588-36-3P 770-31-0P 776-53-4P 17759-30-7P 76360-82-2P
102669-01-2P 105161-35-1P 180532-43-8P 185040-32-8P 402740-25-4P
402740-26-5P 402740-43-6P 402740-45-8P 402740-46-9P 402740-47-0P
402740-48-1P 402740-49-2P 402740-51-6P 402740-54-9P 402740-55-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 7-oxopyridopyrimidines as p38 MAP kinase inhibitors)

L47 ANSWER 17 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:618153 HCAPLUS
TITLE: 4-Azaindoles: Novel inhibitors of p38 MAP kinase
AUTHOR(S): Trejo, Alejandra; Arzeno, Humberto; Browner, Michelle; Cheng, Soan; Comer, Daniel D.; Dalrymple, Stacie; Freire-Moar, Jose; Lim, Julie; McIntosh, Joel; Miller, Jennifer; Myers, Peter L.; Saunders, John; Sjogren, Eric B.; Spellmyer, David; Warren, Stephen D.; Whiteley, Phyllis E.; Zeng, Lu; Goldstein, David M.
CORPORATE SOURCE: Roche Bioscience, Palo Alto, CA, 94304, USA
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), MEDI-302. American Chemical Society: Washington, D. C.
CODEN: 69CZPZ
DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB Regulation of cytokine biosynthesis in various cell types is regulated through activation of p38 MAP kinase including the proinflammatory cytokines interleukin 1 β (IL-1 β) and tumor necrosis factor α (TNF α). Anti IL-1ra and TNF α biologics such as Kineret, Infliximab and Etanercept have clin. validated that modulation of these cytokines leads to dramatic improvement in inflammatory diseases such as rheumatoid arthritis and Crohn's disease. Development of an orally active small mol. inhibitor of p38 is of extreme interest and focus of many pharmaceutical research programs. Initial approaches towards developing novel proprietary leads in the p38 program lead to the synthesis of compds. in the 4-azaindole class which are extremely potent with IC 50's in the low nanomolar range. Synthesis of these compds. along with their biol. activity will be presented.

L47 ANSWER 18 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:300721 HCAPLUS

DOCUMENT NUMBER: 134:326540

TITLE: Preparation of alkylamino substituted bicyclic nitrogen heterocycles for pharmaceutical use as inhibitors of p38 protein kinase

INVENTOR(S): Dunn, James Patrick; Fisher, Lawrence Emerson; Goldstein, David Michael; Harris, William; Hill, Christopher Huw; Smith, Ian Edward David; Welch, Teresa Rosanne

PATENT ASSIGNEE(S): F. Hoffmann-La Roche Ag, Switz.

SOURCE: PCT Int. Appl., 177 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

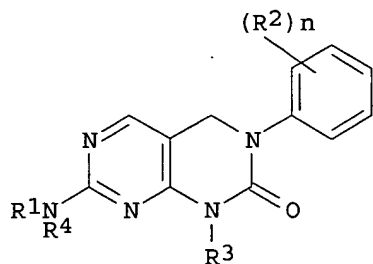
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2001029042 | A1 | 20010426 | WO 2000-EP10088 | 20001013 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2388142 | AA | 20010426 | CA 2000-2388142 | 20001013 |
| BR 2000015243 | A | 20020716 | BR 2000-15243 | 20001013 |
| EP 1228070 | A1 | 20020807 | EP 2000-967864 | 20001013 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| TR 200201057 | T2 | 20020923 | TR 2002-1057 | 20001013 |
| JP 2003512378 | T2 | 20030402 | JP 2001-531840 | 20001013 |
| NZ 518119 | A | 20040227 | NZ 2000-518119 | 20001013 |
| AU 776250 | B2 | 20040902 | AU 2000-77873 | 20001013 |
| RU 2265606 | C2 | 20051210 | RU 2002-112753 | 20001013 |
| US 6451804 | B1 | 20020917 | US 2000-693337 | 20001020 |
| ZA 2002002540 | A | 20030630 | ZA 2002-2540 | 20020328 |
| NO 2002001781 | A | 20020418 | NO 2002-1781 | 20020416 |
| HK 1051039 | A1 | 20050401 | HK 2003-103208 | 20030506 |
| PRIORITY APPLN. INFO.: | | | US 1999-160803P | P 19991021 |
| | | | US 2000-213743P | P 20000622 |

WO 2000-EP10088

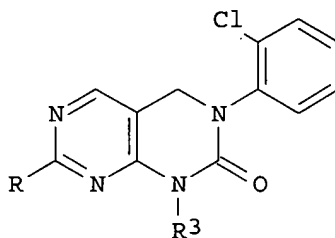
W 20001013

OTHER SOURCE(S):
GI

MARPAT 134:326540



I



II

AB Alkylamino-substituted dihydropyrimido[4,5-d]pyrimidinone derivs., such as I [R1 = H, alkyl, alkenyl, alkynyl, acyl, cycloalkyl, etc.; R2 = vinyl, alkyl, halogen, heteroalkyl; R3 = alkyl, heteroalkyl, cycloalkyl, heterocyclyl, etc.; R4 = H, alkyl, etc.; n = 0-3], were prepared for pharmaceutical use. The compds. are p38 inhibitors and may be used in the treatment of arthritis, Crohn's disease, irritable bowel syndrome, adult respiratory distress syndrome, chronic obstructive pulmonary disease, osteoporosis, or Alzheimer's disease. Thus, dihydropyrimido[4,5-d]pyrimidinone II (R = NHCMe2CH2OH, R3 = Me) was prepared via a substitution reaction of H2NCMe2CH2OH with sulfone II (R = SO2Me, R3 = Me) when combined and heated to 100-110° for 1 h. The prepared dihydropyrimido[4,5-d]pyrimidinone derivs. showed 50% p38 inhibitory activity at concns. < 10 µM.

IC ICM C07D487-04

ICS A61K031-505; A61P029-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 7, 63

IT Anti-inflammatory agents

(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of p38 protein kinase)

| | | | | | |
|----|--------------|--------------|--------------|--------------|--------------|
| IT | 335651-19-9P | 335651-20-2P | 335651-24-6P | 335651-30-4P | 335651-49-5P |
| | 335651-50-8P | 335651-51-9P | 335651-53-1P | 335651-55-3P | 335651-56-4P |
| | 335651-57-5P | 335651-58-6P | 335651-59-7P | 335651-60-0P | 335651-61-1P |
| | 335651-62-2P | 335651-63-3P | 335651-64-4P | 335651-65-5P | 335651-66-6P |
| | 335651-67-7P | 335651-69-9P | 335651-77-9P | 335651-88-2P | 335651-89-3P |
| | 335651-93-9P | 335651-94-0P | 335651-95-1P | 335651-96-2P | 335651-97-3P |
| | 335651-98-4P | 335651-99-5P | 335652-00-1P | 335652-06-7P | 335652-11-4P |
| | 335652-12-5P | 335652-13-6P | 335652-14-7P | 335652-16-9P | 335652-18-1P |
| | 335652-22-7P | 335652-24-9P | 335652-26-1P | 335652-30-7P | 335652-32-9P |
| | 335652-36-3P | 335652-39-6P | 335652-40-9P | 335652-41-0P | 335652-44-3P |
| | 335652-46-5P | 335652-47-6P | 335652-48-7P | 335652-50-1P | 335652-55-6P |
| | 335652-56-7P | 335652-58-9P | 335652-59-0P | 335652-60-3P | 335652-61-4P |
| | 335652-62-5P | 335652-63-6P | 335652-64-7P | 335652-65-8P | 335652-66-9P |
| | 335652-67-0P | 335652-68-1P | | | |

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of p38 protein kinase)

| | | | | | |
|----|--------------|--------------|--------------|--------------|--------------|
| IT | 335651-18-8P | 335651-21-3P | 335651-22-4P | 335651-23-5P | 335651-25-7P |
| | 335651-26-8P | 335651-27-9P | 335651-28-0P | 335651-29-1P | 335651-31-5P |

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|--------------|--------------|--------------|--------------|--------------|
| 335651-32-6P | 335651-33-7P | 335651-34-8P | 335651-36-0P | 335651-37-1P |
| 335651-38-2P | 335651-39-3P | 335651-40-6P | 335651-41-7P | 335651-42-8P |
| 335651-43-9P | 335651-44-0P | 335651-45-1P | 335651-46-2P | 335651-47-3P |
| 335651-48-4P | 335651-52-0P | 335651-54-2P | 335651-68-8P | 335651-70-2P |
| 335651-71-3P | 335651-72-4P | 335651-73-5P | 335651-74-6P | 335651-75-7P |
| 335651-76-8P | 335651-78-0P | 335651-79-1P | 335651-80-4P | 335651-81-5P |
| 335651-82-6P | 335651-83-7P | 335651-84-8P | 335651-85-9P | 335651-86-0P |
| 335651-87-1P | 335651-90-6P | 335651-91-7P | 335651-92-8P | 335652-02-3P |
| 335652-04-5P | 335652-08-9P | 335652-10-3P | 335652-20-5P | 335652-28-3P |
| 335652-34-1P | 335652-37-4P | 335652-38-5P | 335652-42-1P | 335652-43-2P |
| 335652-45-4P | 335652-49-8P | 335652-51-2P | 335652-52-3P | 335652-53-4P |
| 335652-54-5P | 335652-57-8P | 335652-69-2P | 335652-70-5P | 335652-71-6P |
| 335652-72-7P | 335652-73-8P | 335652-74-9P | 335652-75-0P | 335652-76-1P |
| 335652-77-2P | 335652-78-3P | 335652-79-4P | 335652-80-7P | 335652-81-8P |
| 335652-82-9P | 335652-83-0P | 335652-84-1P | 335652-85-2P | 335652-86-3P |
| 335652-87-4P | 335652-88-5P | 335652-90-9P | 335652-91-0P | 335652-92-1P |
| 335652-93-2P | 335652-94-3P | 335652-95-4P | 335652-96-5P | 335652-97-6P |
| 335652-98-7P | 335652-99-8P | 335653-00-4P | 335653-01-5P | 335653-02-6P |
| 335653-03-7P | 335653-04-8P | 335653-05-9P | 335653-06-0P | 335653-07-1P |
| 335653-08-2P | 335653-09-3P | 335653-10-6P | 335653-11-7P | 335653-12-8P |
| 335653-13-9P | 335653-16-2P | 335653-17-3P | 335653-18-4P | 335653-19-5P |
| 335653-20-8P | 335653-21-9P | 335653-22-0P | 335653-23-1P | 335653-24-2P |
| 335653-25-3P | 335653-26-4P | 335653-27-5P | 335653-28-6P | 335653-29-7P |
| 335653-30-0P | 335653-31-1P | 335653-32-2P | 335653-33-3P | 335653-34-4P |
| 335653-35-5P | 335653-36-6P | 335653-37-7P | 335653-38-8P | |

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of p38 protein kinase)

IT 165245-96-5, p38 Kinase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of p38 protein kinase)

IT 62-53-3, Benzenamine, reactions 77-85-0 78-96-6 94-05-3 95-51-2
 95-53-4, reactions 96-32-2 96-33-3 100-37-8 100-39-0 103-49-1
 105-36-2 106-52-5 107-13-1, 2-Propenenitrile, reactions 108-01-0
 115-69-5 124-68-5 540-51-2 556-82-1 590-17-0 608-31-1 614-68-6
 624-75-9 683-57-8 770-31-0 2615-25-0 2675-89-0 2749-11-3
 2955-88-6, 1-Pyrrolidineethanol 3320-83-0 4043-59-8 4313-56-8
 4746-97-8, 1,4-Dioxaspiro[4.5]decan-8-one 5271-38-5 5292-43-3
 5303-65-1 5909-24-0 6168-72-5 6482-24-2 10316-79-7 13360-57-1
 19059-68-8 23735-43-5 25236-64-0 27489-62-9 29943-42-8
 35320-23-1 40525-78-8 50541-93-0 58859-46-4 73579-08-5
 73874-95-0 76513-69-4 89854-94-4 106268-97-7 108102-48-3
 109384-19-2 132431-09-5 144222-22-0 164646-07-5

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of p38 protein kinase)

IT 774-07-2P 776-53-4P 7149-62-4P 17759-30-7P 18511-56-3P
 38041-19-9P 61128-73-2P 76360-82-2P 97096-16-7P,
 1,4-Dioxaspiro[4.5]decan-8-amine 100193-64-4P 106475-47-2P
 138876-37-6P 180918-12-1P 185040-32-8P 187217-99-8P 211245-55-5P
 211245-56-6P 266313-81-9P 266313-82-0P 266313-83-1P 266313-84-2P
 266315-45-1P 335318-13-3P 335318-14-4P 335318-20-2P 335318-29-1P
 335318-30-4P 335653-39-9P 335653-40-2P 335653-41-3P 335653-42-4P
 335653-43-5P 335653-44-6P 335653-45-7P 335653-46-8P 335653-47-9P
 335653-48-0P 335653-49-1P 335653-50-4P 335653-51-5P 335653-52-6P
 335653-53-7P 335653-54-8P 335653-55-9P 335653-56-0P 335653-57-1P

335653-58-2P 335653-59-3P 335653-60-6P 335653-61-7P 335653-62-8P
 335653-63-9P 335653-64-0P 335653-65-1P 335653-66-2P 335653-67-3P
 335653-68-4P 335653-69-5P 335653-70-8P 335653-71-9P 335653-72-0P
 335653-73-1P 335653-74-2P 335653-75-3P 335653-76-4P 335653-77-5P
 335653-78-6P 335653-79-7P 335653-80-0P 335653-81-1P 335653-82-2P
 335653-83-3P 335653-84-4P 335653-85-5P

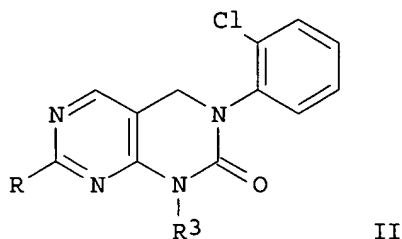
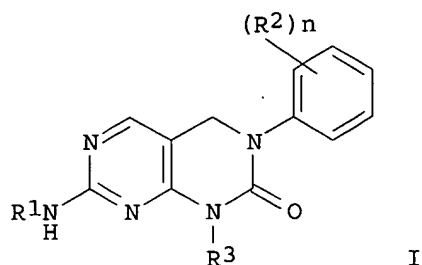
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of p38 protein kinase)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 19 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2001:300720 HCAPLUS
 DOCUMENT NUMBER: 134:311223
 TITLE: Preparation of alkylamino substituted bicyclic nitrogen heterocycles for pharmaceutical use as inhibitors of p38 protein kinase
 INVENTOR(S): Dunn, James Patrick; Goldstein, David Michael; Harris, William; Smith, Ian Edward David; Welch, Teresa Rosanne
 PATENT ASSIGNEE(S): F. Hoffmann-La Roche Ag, Switz.
 SOURCE: PCT Int. Appl., 59 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-------------------|------------|
| WO 2001029041 | A1 | 20010426 | WO 2000-EP10077 | 20001013 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2388140 | AA | 20010426 | CA 2000-2388140 | 20001013 |
| BR 2000014973 | A | 20020716 | BR 2000-14973 | 20001013 |
| TR 200201058 | T2 | 20020722 | TR 2002-1058 | 20001013 |
| EP 1226144 | A1 | 20020731 | EP 2000-972755 | 20001013 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| JP 2003512377 | T2 | 20030402 | JP 2001-531839 | 20001013 |
| AU 776695 | B2 | 20040916 | AU 2001-11375 | 20001013 |
| RU 2264404 | C2 | 20051120 | RU 2002-110286 | 20001013 |
| US 6642241 | B1 | 20031104 | US 2000-693364 | 20001020 |
| ZA 2002002603 | A | 20030703 | ZA 2002-2603 | 20020403 |
| NO 2002001783 | A | 20020416 | NO 2002-1783 | 20020416 |
| HK 1051040 | A1 | 20050128 | HK 2003-103209 | 20030506 |
| PRIORITY APPLN. INFO.: | | | US 1999-160804P | P 19991021 |
| | | | US 2000-213718P | P 20000622 |
| | | | WO 2000-EP10077 | W 20001013 |
| OTHER SOURCE(S): | | | MARPAT 134:311223 | |
| GI | | | | |



AB Alkylamino-substituted dihydropyrimido[4,5-d]pyrimidinone derivs., such as I [R1 = H, alkyl, alkenyl, alkynyl, acyl, cycloalkyl, etc.; R2 = vinyl, alkyl, halogen, heteroalkyl; R3 = alkyl, heteroalkyl, cycloalkyl, heterocyclyl, etc.; n = 0-3], were prepared for pharmaceutical use as inhibitors of p38 protein kinase for the treatment of conditions such as arthritis, Crohn's disease, obstructive pulmonary disease, or irritable bowel syndrome.. Thus, dihydropyrimido[4,5-d]pyrimidinone II (R = NHCHMe2, R3 = CH2CO2H) was prepared via a substitution reaction of H2NCHMe2 with sulfone II (R = SO2CH2Ph, R3 = CH2CO2Et) when combined and heated to 90-100° for 1 h. The prepared dihydropyrimido[4,5-d]pyrimidinone derivs. showed p38 50% inhibitory activity at concns. < 10 µM.

IC ICM C07D487-04

ICS A61K031-505; A61P029-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1, 7, 63

IT Anti-inflammatory agents

(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of p38 protein kinase)

IT 335318-15-5P 335318-19-9P 335318-22-4P 335318-39-3P 335318-40-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of p38 protein kinase)

IT 335318-09-7P 335318-10-0P 335318-11-1P 335318-12-2P 335318-16-6P
335318-17-7P 335318-18-8P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of p38 protein kinase)

IT 165245-96-5, p38 Kinase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of p38 protein kinase)

IT 62-56-6, Thiourea, reactions 75-31-0, 2-Propanamine, reactions 94-05-3
95-51-2 100-39-0 105-36-2 109-86-4 3040-44-6, 1-Piperidineethanol
5271-38-5 23735-43-5 23788-74-1 93550-77-7

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for pharmaceutical use as inhibitors of p38 protein kinase)

IT 774-07-2P 7149-62-4P 100193-64-4P 335318-13-3P 335318-14-4P
335318-20-2P 335318-21-3P 335318-23-5P 335318-24-6P 335318-25-7P
335318-26-8P 335318-27-9P 335318-29-1P 335318-30-4P 335318-31-5P

335318-32-6P 335318-33-7P 335318-34-8P 335318-35-9P 335318-36-0P
335318-37-1P 335318-38-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)

(preparation of alkylamino substituted pyrimidino[4,5-d]pyrimidines for
pharmaceutical use as inhibitors of p38 protein kinase)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 20 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:228861 HCAPLUS

DOCUMENT NUMBER: 134:266303

TITLE: Preparation of 5-amino-4-aryloxy-1-arylpyrazoles as
p-38 MAP kinase inhibitors.

INVENTOR(S): Goldstein, David Michael; Labadie, Sharada
Shenvi; Rotstein, David Mark; Sjogren, Eric Brian;
Talamas, Francisco Xavier

PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.

SOURCE: PCT Int. Appl., 112 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

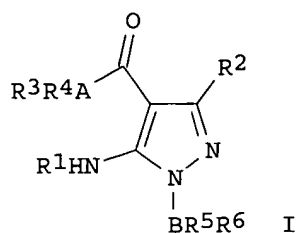
FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|-------------|
| WO 2001021591 | A1 | 20010329 | WO 2000-EP8981 | 20000914 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, | | | | |
| DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, | | | | |
| JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, | | | | |
| MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, | | | | |
| TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, | | | | |
| DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, | | | | |
| CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 6316466 | B1 | 20011113 | US 1999-401141 | 19990922 |
| CA 2385447 | AA | 20010329 | CA 2000-2385447 | 20000914 |
| BR 2000014225 | A- | 20020521 | BR 2000-14225 | 20000914 |
| EP 1218346 | A1 | 20020703 | EP 2000-966008 | 20000914 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, | | | | |
| IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| JP 2003509495 | T2 | 20030311 | JP 2001-524971 | 20000914 |
| AU 777470 | B2 | 20041021 | AU 2000-76558 | 20000914 |
| PRIORITY APPLN. INFO.: | | | US 1999-401141 | A 19990922 |
| | | | US 1998-84250P | P 19980505 |
| | | | US 1999-122410P | P 19990302 |
| | | | US 1999-130369P | P 19990421 |
| | | | US 1999-305737 | A2 19990505 |
| | | | WO 2000-EP8981 | W 20000914 |

OTHER SOURCE(S): MARPAT 134:266303

GI



AB Title compds. [I; R1 = H, acyl; A, B = aryl, heteroaryl; R3 = amino, acylamino, (substituted) heterocyclyl, aryl, heteroaryl, heteroalkyl, etc.; R4 = H, halo, alkyl, alkoxy, OH; R5 = H, halo, alkyl, haloalkyl, OH, amino, thioalkyl, heteroalkyl, (substituted) heterocyclyl, etc.; R6 = H, halo, alkyl, alkoxy], were prepared Thus, 5-amino-4-(3-bromobenzoyl)-1-(4-fluorophenyl)pyrazole (preparation given), 4-(2-propynyl)morpholine (preparation

given), (PPh₃)₂PdCl₂, and CuI were heated in diisopropylamine at 70° for 10 h to give 5-amino-1-(4-fluorophenyl)-4-[3-(3-morpholin-4-ylprop-1-ynyl)benzoyl]pyrazole hydrochloride. Tested I inhibited LPS-induced TNFα production in THP1 cells with IC₅₀ = 0.17-1.77 μM.

IC ICM C07D231-38

ICS C07D413-10; C07D403-10; C07D401-10; C07D413-12; C07D401-12; C07D409-06; C07D405-06; C07D401-06; C07D405-12; A61K031-415; C07D413-10; C07D265-00; C07D231-00; C07D403-10; C07D241-00; C07D231-00

CC 28-8 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

IT Anti-inflammatory agents

Antiarthritics

(preparation of aminoaroylarylpyrazoles as p-38 MAP kinase inhibitors)

IT Tumor necrosis factors

RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)

(production inhibitors; preparation of aminoaroylarylpyrazoles as p-38 MAP kinase inhibitors)

IT 165245-96-5, p-38 MAP kinase

RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)

(inhibitors; preparation of aminoaroylarylpyrazoles as p-38 MAP kinase inhibitors)

IT 249935-56-6P 249935-63-5P 249935-94-2P 249936-51-4P 249936-54-7P

249936-65-0P 249937-47-1P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of aminoaroylarylpyrazoles as p-38 MAP kinase inhibitors)

IT 249935-54-4P 249935-55-5P 249935-57-7P 249935-58-8P 249935-59-9P

249935-60-2P 249935-61-3P 249935-62-4P 249935-64-6P 249935-66-8P

249935-67-9P 249935-68-0P 249935-69-1P 249935-70-4P 249935-71-5P

249935-72-6P 249935-73-7P 249935-74-8P 249935-75-9P 249935-76-0P

249935-77-1P 249935-78-2P 249935-79-3P 249935-80-6P 249935-81-7P

249935-82-8P 249935-83-9P 249935-84-0P 249935-85-1P 249935-86-2P

249935-87-3P 249935-88-4P 249935-89-5P 249935-90-8P 249935-91-9P

249935-92-0P 249935-93-1P 249935-95-3P 249935-96-4P 249935-97-5P

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|--------------|--------------|--------------|--------------|--------------|
| 249935-98-6P | 249935-99-7P | 249936-00-3P | 249936-01-4P | 249936-02-5P |
| 249936-03-6P | 249936-04-7P | 249936-05-8P | 249936-06-9P | 249936-07-0P |
| 249936-08-1P | 249936-09-2P | 249936-10-5P | 249936-11-6P | 249936-12-7P |
| 249936-13-8P | 249936-14-9P | 249936-15-0P | 249936-16-1P | 249936-17-2P |
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| 249936-30-9P | 249936-31-0P | 249936-32-1P | 249936-33-2P | 249936-34-3P |
| 249936-35-4P | 249936-36-5P | 249936-37-6P | 249936-38-7P | 249936-39-8P |
| 249936-40-1P | 249936-41-2P | 249936-42-3P | 249936-43-4P | 249936-44-5P |
| 249936-45-6P | 249936-46-7P | 249936-47-8P | 249936-48-9P | 249936-49-0P |
| 249936-50-3P | 249936-52-5P | 249936-53-6P | 249936-55-8P | 249936-56-9P |
| 249936-57-0P | 249936-58-1P | 249936-59-2P | 249936-60-5P | 249936-61-6P |
| 249936-62-7P | 249936-63-8P | 249936-64-9P | 249936-66-1P | 249936-67-2P |
| 249936-68-3P | 249936-69-4P | 249936-70-7P | 249936-71-8P | 249936-73-0P |
| 249936-74-1P | 249936-75-2P | 249936-76-3P | 249936-77-4P | 249936-78-5P |
| 249936-79-6P | 249936-80-9P | 249936-81-0P | 249936-82-1P | 249936-83-2P |
| 249936-85-4P | 249936-87-6P | 249936-89-8P | 249936-90-1P | 249936-91-2P |
| 249936-92-3P | 249936-93-4P | 249936-94-5P | 249936-95-6P | 249936-96-7P |
| 249936-97-8P | 249937-14-2P | 249937-23-3P | 331777-09-4P | 331777-10-7P |
| 331777-11-8P | 331777-12-9P | 331777-13-0P | 331777-14-1P | 331777-18-5P |
| 331777-19-6P | 331777-20-9P | 331777-21-0P | 331777-22-1P | 331777-23-2P |
| 331777-24-3P | 331777-25-4P | 331777-26-5P | 331777-27-6P | 331777-28-7P |
| 331777-29-8P | 331777-30-1P | 331777-31-2P | | |

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of aminoaroylarylpyrazoles as p-38 MAP kinase inhibitors)

IT 74-89-5, Methylamine, reactions 75-05-8, Acetonitrile, reactions 79-14-1, Glycolic acid, reactions 79-22-1, Methyl chloroformate 94-05-3, Ethyl ethoxymethylenecyanoacetate 100-63-0, Phenylhydrazine 106-96-7, Propargyl bromide 109-01-3, N-Methylpiperazine 109-70-6, 1-Bromo-3-chloropropane 109-89-7, Diethylamine, reactions 110-89-4, Piperidine, reactions 110-91-8, Morpholine, reactions 111-42-2, Diethanolamine, reactions 111-95-5 124-40-3, Dimethylamine, reactions 141-43-5, 2-Aminoethanol, reactions 371-14-2, 4-Fluorophenylhydrazine 462-08-8, 3-Aminopyridine 504-29-0, 2-Aminopyridine 504-30-3, 3(2H)-Pyridazinone 540-51-2, 2-Bromoethanol 586-98-1, 2-Pyridinemethanol 614-16-4, Benzoylacetonitrile 615-00-9, 2,4-Dimethylphenylhydrazine 618-91-7, Methyl 3-iodobenzoate 626-55-1, 3-Bromopyridine 658-27-5, 3-Fluorophenylhydrazine 693-98-1, 2-Methylimidazole 822-36-6, 4-Methylimidazole 877-66-7, 4-Methylsulfonylphenylhydrazine 1711-09-7 1795-48-8, Isopropyl isocyanate 1820-80-0, 3-Aminopyrazole 1878-67-7, 3-Bromophenylacetic acid 2127-03-9, 2-Aldrithiol 2339-53-9, 3-Fluoro-6-methylphenylhydrazine 2386-58-5, Vinyl sulfonamide 2398-37-0, 3-Bromoanisole 2402-97-3, 3-Bromopyridine N-oxide 3445-11-2 3471-32-7, 4-Methoxyphenylhydrazine 3647-69-6, 4-(2-Chloroethyl)morpholine hydrochloride 5292-43-3, tert-Butyl bromoacetate 5382-16-1, 4-Hydroxypiperidine 7486-35-3, Vinyltributyltin 18312-46-4, 2-Methoxyphenylhydrazine 19275-55-9, 2-Ethylphenylhydrazine 19438-10-9, Methyl 3-hydroxybenzoate 23788-74-1 51304-65-5, 3-Chloro-4-methylphenylhydrazine 51934-41-9, Ethyl 4-iodobenzoate 58791-94-9 63693-65-2, 4-Isopropylphenylhydrazine 97674-02-7, Tributyl(1-ethoxyvinyl)tin 124252-41-1 131534-65-1, Pyridine-3-boronic acid, 1,3-propanediol cyclic ester 249937-03-9 249937-48-2 331777-17-4

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of aminoaroylarylpyrazoles as p-38 MAP kinase inhibitors)

IT 5799-76-8P 21667-64-1P 28229-69-8P 70591-86-5P 79601-27-7P
 138907-68-3P 183158-31-8P 187949-90-2P 247206-80-0P 249936-98-9P
 249936-99-0P 249937-00-6P 249937-02-8P 249937-05-1P 249937-06-2P
 249937-07-3P 249937-08-4P 249937-09-5P 249937-10-8P 249937-11-9P
 249937-12-0P 249937-13-1P 249937-16-4P 249937-18-6P 249937-21-1P
 249937-22-2P 249937-25-5P 249937-44-8P 249937-45-9P 331777-15-2P
 331777-16-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)

(preparation of aminoaroylarylpurazoles as p-38 MAP
 kinase inhibitors)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 21 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:830885 HCAPLUS

DOCUMENT NUMBER: 135:357921

TITLE: Preparation of 5-amino-4-aryoyl-1-arylpurazoles as
 p-38 MAP kinase inhibitors.

INVENTOR(S): Goldstein, David Michael; Labadie, Sharada
 Shenvi; Rotstein, David Mark; Sjogren, Eric Brian;
 Talamas, Francisco Xavier

PATENT ASSIGNEE(S): Syntex (U.S.A.) Llc, USA

SOURCE: U.S., 41 pp., Cont.-in-part of U.S. Ser. No. 305,737.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

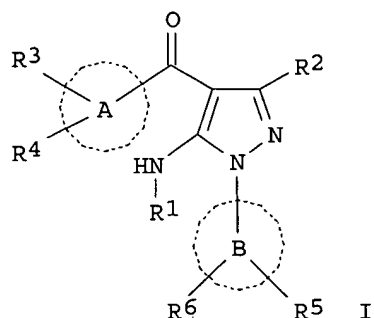
FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| US 6316466 | B1 | 20011113 | US 1999-401141 | 19990922 |
| US 6376527 | B1 | 20020423 | US 1999-305737 | 19990505 |
| CA 2385447 | AA | 20010329 | CA 2000-2385447 | 20000914 |
| WO 2001021591 | A1 | 20010329 | WO 2000-EP8981 | 20000914 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| BR 2000014225 | A | 20020521 | BR 2000-14225 | 20000914 |
| TR 200200778 | T2 | 20020621 | TR 2002-778 | 20000914 |
| EP 1218346 | A1 | 20020703 | EP 2000-966008 | 20000914 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| JP 2003509495 | T2 | 20030311 | JP 2001-524971 | 20000914 |
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| US 6444696 | B2 | 20020903 | | |
| US 2002156114 | A1 | 20021024 | US 2002-45903 | 20020111 |
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| US 6979693 | B2 | 20051227 | | |
| ZA 2002001559 | A | 20030526 | ZA 2002-1559 | 20020225 |
| PRIORITY APPLN. INFO.: | | | US 1998-84250P | P 19980505 |
| | | | US 1999-122410P | P 19990302 |

| | |
|-----------------|-------------|
| US 1999-130369P | P 19990421 |
| US 1999-305737 | A2 19990505 |
| US 1999-401141 | A 19990922 |
| WO 2000-EP8981 | W 20000914 |

OTHER SOURCE(S): MARPAT 135:357921
GI



AB Title compds. [I; R1 = H, acyl; R2 = H, alkyl; A, B = aryl, heteroaryl; R3 = amino, acylamino, (substituted) heterocyclyl, aryl, heteroaryl, heteroalkyl, etc.; R4 = H, halo, alkyl, alkoxy, OH; R5 = H, halo, alkyl, haloalkyl, OH, amino, etc.; R6 = H, halo, alkyl, alkoxy], were prepared and formulated. Thus, 5-amino-4-(3-bromobenzoyl)-1-(4-fluorophenyl)pyrazole (preparation given), 4-(2-propynyl)morpholine (preparation given), (PPh₃)₂PdCl₂, and

CuI were heated in diisopropylamine at 70° for 10 h to give 5-amino-1-(4-fluorophenyl)-4-[3-(3-morpholin-4-ylprop-1-ynyl)benzoyl]pyrazole hydrochloride. Tested I inhibited LPS-induced TNF α production in THP1 cells with IC₅₀ = 0.17-1.77 μ M.

IC A61K031-4155; A61K031-4709; C07D401-06; C07D405-06; C07D409-06

INCL 514314000

CC 28-8 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63

IT Anti-inflammatory agents
Antiarthritics

(preparation of aminoaroylarylpyrazoles as p-38 MAP kinase inhibitors)

IT Tumor necrosis factors
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(production inhibitors; preparation of aminoaroylarylpyrazoles as p-38 MAP kinase inhibitors)

IT 165245-96-5, p-38 MAP kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(inhibitors; preparation of aminoaroylarylpyrazoles as p-38 MAP kinase inhibitors)

IT 249935-56-6P 249935-63-5P 249935-94-2P 249936-51-4P 249936-54-7P
249936-65-0P 249937-47-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of aminoaroylarylpyrazoles as p-38 MAP kinase inhibitors)

IT 249935-54-4P 249935-55-5P 249935-57-7P 249935-58-8P 249935-59-9P

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| 249935-60-2P | 249935-61-3P | 249935-62-4P | 249935-64-6P | 249935-66-8P |
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| 249935-72-6P | 249935-73-7P | 249935-74-8P | 249935-75-9P | 249935-76-0P |
| 249935-77-1P | 249935-78-2P | 249935-79-3P | 249935-80-6P | 249935-81-7P |
| 249935-82-8P | 249935-83-9P | 249935-84-0P | 249935-85-1P | 249935-86-2P |
| 249935-87-3P | 249935-88-4P | 249935-89-5P | 249935-90-8P | 249935-91-9P |
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| 249936-62-7P | 249936-63-8P | 249936-64-9P | 249936-66-1P | 249936-67-2P |
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| 249936-79-6P | 249936-80-9P | 249936-81-0P | 249936-82-1P | 249936-83-2P |
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| 331777-29-8P | 331777-30-1P | 331777-31-2P | | |

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of aminoaroylarylpyrazoles as p-38 MAP kinase inhibitors)

IT 74-89-5, Methylamine, reactions 75-05-8, Acetonitrile, reactions
 79-14-1, Glycolic acid, reactions 79-22-1, Methyl chloroformate
 94-05-3, Ethyl ethoxymethylenecyanoacetate 100-63-0, Phenylhydrazine
 106-96-7, Propargyl bromide 109-01-3, N-Methylpiperazine 109-70-6,
 1-Bromo-3-chloropropane 109-89-7, Diethylamine, reactions 110-89-4,
 Piperidine, reactions 110-91-8, Morpholine, reactions 111-42-2,
 Diethanolamine, reactions 111-95-5 124-40-3, Dimethylamine, reactions
 141-43-5, 2-Aminoethanol, reactions 371-14-2, 4-Fluorophenylhydrazine
 462-08-8, 3-Aminopyridine 504-29-0, 2-Aminopyridine 504-30-3,
 3(2H)-Pyridazinone 540-51-2, 2-Bromoethanol 586-98-1,
 2-Pyridinemethanol 614-16-4, Benzoylacetonitrile 615-00-9,
 2,4-Dimethylphenylhydrazine 618-91-7, Methyl 3-iodobenzoate 626-55-1,
 3-Bromopyridine 658-27-5, 3-Fluorophenylhydrazine 693-98-1,
 2-Methylimidazole 822-36-6, 4-Methylimidazole 877-66-7,
 4-Methylsulfonylphenylhydrazine 1711-09-7 1795-48-8, Isopropyl
 isocyanate 1820-80-0, 3-Aminopyrazole 1878-67-7, 3-Bromophenylacetic
 acid 2127-03-9, 2-Aldrithiol 2339-53-9, 3-Fluoro-6-
 methylphenylhydrazine 2386-58-5, Vinyl sulfonamide 2398-37-0,
 3-Bromoanisole 2402-97-3, 3-Bromopyridine N-oxide 3445-11-2
 3471-32-7, 4-Methoxyphenylhydrazine 3647-69-6, 4-(2-
 Chloroethyl)morpholine hydrochloride 5292-43-3, tert-Butyl bromoacetate
 5382-16-1, 4-Hydroxypiperidine 7486-35-3, Vinyltributyltin 18312-46-4,
 2-Methoxyphenylhydrazine 19275-55-9, 2-Ethylphenylhydrazine
 19438-10-9, Methyl 3-hydroxybenzoate 23788-74-1 51304-65-5,
 3-Chloro-4-methylphenylhydrazine 51934-41-9, Ethyl 4-iodobenzoate

58791-94-9 63693-65-2, 4-Isopropylphenylhydrazine 97674-02-7,
Tributyl(1-ethoxyvinyl)tin 124252-41-1 131534-65-1, Pyridine-3-boronic
acid, 1,3-propanediol cyclic ester 249937-03-9 249937-48-2
331777-17-4

RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of aminoarylpyrazoles as p-38 MAP
kinase inhibitors)

IT 5799-76-8P 21667-64-1P 28229-69-8P 70591-86-5P 79601-27-7P
138907-68-3P 183158-31-8P 187949-90-2P 247206-80-0P 249936-98-9P
249936-99-0P 249937-00-6P 249937-02-8P 249937-05-1P 249937-06-2P
249937-07-3P 249937-08-4P 249937-09-5P 249937-10-8P 249937-11-9P
249937-12-0P 249937-13-1P 249937-16-4P 249937-18-6P 249937-21-1P
249937-22-2P 249937-25-5P 249937-44-8P 249937-45-9P 331777-15-2P
331777-16-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(preparation of aminoarylpyrazoles as p-38 MAP
kinase inhibitors)

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 22 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:331893 HCAPLUS

TITLE: Oxindolylidene derivatives as p38 MAP kinase
inhibitors.

AUTHOR(S): Cheng, Soan; Comer, Daniel, D.; Freire-Moar, Jose;
Goldstein, David, M.; Myers, Peter, L.;
Saunders, John; Sjogren, Eric, B.; Teig, Steve;
Warren, Stephen; Whiteley, Phyllis, E.

CORPORATE SOURCE: Department of Medicinal Chemistry, CombiChem, Inc, San
Diego, CA, 92121, USA

SOURCE: Book of Abstracts, 219th ACS National Meeting, San
Francisco, CA, March 26-30, 2000 (2000), MEDI-282.
American Chemical Society: Washington, D. C.
CODEN: 69CLAC

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB Abstract: Several series of oxindolylidene derivs. were prepared for
evaluation as p38 MAP kinase inhibitors. Base-catalyzed condensations of
oxindoles with carbonyl compds. led to the formation of oxindolylidene
derivs. The introduction of the benzoyl group at the 6-position of
oxindoles is effective in obtaining potent analogs. Various arylidene and
heteroarylidene groups at the C-3 position were evaluated. This work has
resulted in several novel potent structures as p38 MAP kinase inhibitors.
The most potent analog of the oxindole series is CC-8866, with an IC50 of
0.14 μ M.

L47 ANSWER 23 OF 24 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:282215 HCAPLUS

DOCUMENT NUMBER: 130:325138

TITLE: Preparation of pyrrolopyridines, furopyridines, and
related compounds as p-38 MAP
kinase inhibitors.

INVENTOR(S): Cheng, Soan; Goldstein, David Michael;
Martin, Teresa Alejandra Trejo; Sjogren, Eric Brian

PATENT ASSIGNEE(S): F.Hoffmann-La Roche A.-G., Switz.

SOURCE: PCT Int. Appl., 152 pp.

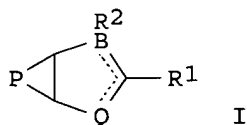
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-------------------|----------|
| WO 9920624 | A1 | 19990429 | WO 1998-EP6472 | 19981013 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW | | | | |
| RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2306870 | AA | 19990429 | CA 1998-2306870 | 19981013 |
| AU 9897499 | A1 | 19990510 | AU 1998-97499 | 19981013 |
| AU 745579 | B2 | 20020321 | | |
| TR 200001079 | T2 | 20000721 | TR 2000-200001079 | 19981013 |
| BR 9812944 | A | 20000808 | BR 1998-12944 | 19981013 |
| EP 1025102 | A1 | 20000809 | EP 1998-951516 | 19981013 |
| EP 1025102 | B1 | 20040519 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| JP 2001520227 | T2 | 20011030 | JP 2000-516966 | 19981013 |
| JP 3579350 | B2 | 20041020 | | |
| RU 2219178 | C2 | 20031220 | RU 2000-110738 | 19981013 |
| AT 267200 | E | 20040615 | AT 1998-951516 | 19981013 |
| ES 2221213 | T3 | 20041216 | ES 1998-951516 | 19981013 |
| US 6316464 | B1 | 20011113 | US 1998-174299 | 19981016 |
| ZA 9809529 | A | 19990420 | ZA 1998-9529 | 19981019 |
| TW 224596 | B1 | 20041201 | TW 1998-87117244 | 19981019 |
| HR 2000000209 | A1 | 20010430 | HR 2000-209 | 20000412 |
| NO 2000001940 | A | 20000413 | NO 2000-1940 | 20000413 |
| NO 316734 | B1 | 20040419 | | |
| MX 200003810 | A | 20001113 | MX 2000-3810 | 20000418 |
| US 2001044538 | A1 | 20011122 | US 2001-839712 | 20010419 |
| US 6479507 | B2 | 20021112 | | |
| US 2002013354 | A1 | 20020131 | US 2001-839710 | 20010419 |
| US 6630485 | B2 | 20031007 | | |
| US 2003139462 | A1 | 20030724 | US 2002-245906 | 20020917 |
| PRIORITY APPLN. INFO.: | | | | |
| US 1997-62548P P 19971020 | | | | |
| US 1998-75515P P 19980220 | | | | |
| US 1998-96916P P 19980818 | | | | |
| WO 1998-EP6472 W 19981013 | | | | |
| US 1998-174299 A3 19981016 | | | | |
| US 2001-839712 A1 20010419 | | | | |
| OTHER SOURCE(S): MARPAT 130:325138 | | | | |
| GI | | | | |



AB Title compds. [I; R1 = heteroaryl; when the dotted line is a double bond between Q and CR1, then B = N, R2 = aryl, and Q = CR; R = H, alkyl,

haloalkyl, cycloalkyl, NO₂, cyano, amino, acylamino, etc.; when the dotted line = double bond between B and CR1, then B = C; R2 = aryl, heteroaryl; Q = imino, O, S; P = atoms to form (substituted) pyrido, pyridazino, pyrimidino, pyrazino rings], were prepared. Thus, Me isonicotinate and 4-fluorophenylacetonitrile in EtOH were added to a solution prepared from EtOH and Na metal followed by 3 h reflux to give 2-(4-fluorophenyl)-1-(pyridin-4-yl)ethanone. The latter was azeotroped with 3-amino-2-chloropyridine and p-TsOH in PhMe to give (2-chloropyridin-3-yl)-[2-(4-fluorophenyl)-1-(pyridin-4-yl)vinyl]amine. This was heated with DABCO and (Ph₃P)PdCl₂ in DMF to give 3-(4-fluorophenyl)-2-(pyridin-4-yl)-1H-pyrrolo[3,2-b]pyridine. Tested I inhibited p-38 kinase with IC₅₀ = 68-246 nM.

IC ICM C07D471-04
ICS A61K031-435; A61K031-495; C07D491-048; C07D487-04; C07D495-04;
C07D213-74; C07D213-75; C07D213-26; C07D213-70; C07D237-20;
C07D241-18; C07D471-04; C07D221-00; C07D209-00; C07D491-048;
C07D307-00; C07D221-00; C07D487-04; C07D241-00
CC 28-2 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
IT Anti-inflammatory agents
(preparation of pyrrolopyridines, furopyridines, and related compds. as
p-38 MAP kinase inhibitors)
IT Tumor necrosis factors
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC
(Miscellaneous); BIOL (Biological study); PROC (Process)
(production inhibitors; preparation of pyrrolopyridines, furopyridines, and
related compds. as p-38 MAP kinase inhibitors)
IT 165245-96-5, p-38 MAP kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC
(Miscellaneous); BIOL (Biological study); PROC (Process)
(inhibitors; preparation of pyrrolopyridines, furopyridines, and related
compds. as p-38 MAP kinase inhibitors)
IT 223740-58-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU
(Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT
(Reactant or reagent); USES (Uses)
(preparation of pyrrolopyridines, furopyridines, and related compds. as
p-38 MAP kinase inhibitors)
IT 223738-89-4P 223738-90-7P 223738-91-8P 223738-92-9P 223738-93-0P
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 223742-60-7P 223742-64-1P 223742-68-5P 223743-45-1P 223743-47-3P
 223743-48-4P 223743-49-5P 223743-52-0P 223743-53-1P 223743-54-2P
 223743-56-4P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of pyrrolopyridines, furopyridines, and related compds. as p-38 MAP kinase inhibitors)

IT 105-36-2, Ethyl bromoacetate 109-70-6, 1-Chloro-3-bromopropane
 156-87-6, 3-Amino-1-propanol 352-11-4, 4-Fluorobenzyl chloride
 459-22-3, 4-Fluorophenylacetoneitrile 822-36-6, 4-Methylimidazole
 874-24-8, 3-Hydroxypicolinic acid 1120-87-2, 4-Bromopyridine
 1122-54-9, 4-Acetylpyridine 2008-75-5, 1-(2-Chloroethyl)piperidine
 hydrochloride 2459-09-8, Methyl isonicotinate 3647-69-6 5470-18-8,
 2-Chloro-3-nitropyridine 6298-19-7, 3-Amino-2-chloropyridine
 6313-54-8, 2-Chloropyridine-4-carboxylic acid 14254-57-0, Isonicotinoyl
 chloride 14508-49-7, Chloropyrazine 17282-00-7, 2-Amino-3-bromo-5-
 methylpyridine 58481-11-1, Methyl 2-chloropyridine-4-carboxylate
 70298-89-4 116332-54-8 130387-74-5, 4-Fluorophenylmagnesium chloride
 223743-44-0 223743-46-2

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of pyrrolopyridines, furopyridines, and related compds. as p-38 MAP kinase inhibitors)

IT 54608-52-5P 73406-50-5P, Ethyl 3-hydroxypicolinate 115858-98-5P
 223742-77-6P 223742-81-2P 223742-86-7P 223742-89-0P 223742-93-6P
 223742-96-9P 223743-01-9P 223743-04-2P 223743-07-5P 223743-09-7P
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 223743-37-1P 223743-38-2P 223743-39-3P 223743-42-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of pyrrolopyridines, furopyridines, and related compds. as p-38 MAP kinase inhibitors)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 24 OF 24 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2005-656837 [67] WPIX
 DOC. NO. CPI: C2005-198580
 TITLE: New heteroaryl-fused pyrazolo derivatives are p38 kinase inhibitors useful to treat e.g. arthritis, Crohn's disease, Alzheimer's disease, influenza, multiple sclerosis, cancer, diabetes and psoriasis.
 DERWENT CLASS: B02
 INVENTOR(S): ARORA, N; BILLEDEAU, R J; DEWDNEY, N J; GABRIEL, T; GOLDSTEIN, D M; MCCALEB, K L; SOTH, M; TREJO-MARTIN, T A
 PATENT ASSIGNEE(S): (ROCH-N) ROCHE PALO ALTO LLC; (HOFF) HOFFMANN LA ROCHE & CO AG F; (MCCA-I) MCCALEB K L
 COUNTRY COUNT: 109
 PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|------|----------|-----------|----|----|
| US 2005203091 | A1 | 20050915 | (200567)* | | 64 |
| WO 2005085248 | A1 | 20050915 | (200567) | EN | |
| RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW | | | | | |
| W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW | | | | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---------------|----------------|-----------------|----------|
| US 2005203091 | A1 Provisional | US 2004-548642P | 20040227 |
| | | US 2005-65890 | 20050225 |
| WO 2005085248 | A1 | WO 2005-EP1815 | 20050222 |

PRIORITY APPLN. INFO: US 2004-548642P 20040227; US
2005-65890 20050225

AN 2005-656837 [67] WPIX

AB US2005203091 A UPAB: 20051019

NOVELTY - Heteroaryl-fused pyrazolo derivatives (I) and their salts, solvates or prodrugs are new.

DETAILED DESCRIPTION - Heteroaryl-fused pyrazolo derivatives of formula (I) and their salts, solvates or prodrugs are new.

R1 = (hetero)aryl (optionally substituted) or cycloalkyl;

R2 = (hetero)aryl (optionally substituted), cycloalkyl, branched alkyl, iodo or heterocyclyl;

R3, R6, R9 = H or alkyl;

X, Y, Z = N or CR;

R4 = H, alkyl, halo, amino, alkoxy, hydroxy, cyano, heteroalkyl, heterocyclyl, hydroxycycloalkyl or -C(=O)-R5;

R5, R10 = hydroxy, alkoxy, amino, (hetero)alkyl, aralkyl, (hetero)aryl or heterocyclyl;

A = O, CH₂, S(O)_n, C(=O), CH₂(OR₆), NR₇ or CH₂NR₇; either

R₇ = H or alkyl; or

R₁+R₇ = heterocyclyl;

n, j = 0-2;

k = 0 or 1;

B = O, NR₈, S(O)_j, CH(OR₉), CH=CH or C(=O);

R₈ = H, alkyl or -C(=O)-R₁₀; and

R₁₁ = alkyl.

Provided that when A is NR₆, R₁ is not 5-methanesulfonyl-2-methoxyphenyl; and one or two of X, Y, Z is N.

ACTIVITY - Antiarthritic; Antiinflammatory; Gastrointestinal-Gen.; Respiratory-Gen.; Neuroprotective; Nootropic; Virucide; Cytostatic; Antidiabetic; Dermatological; Immunosuppressive; Antipsoriatic; Vulnerary; Antiulcer; Ophthalmological; Antiangiogenic; Nephrotropic; Cardiovascular-Gen.; Gynecological; Analgesic; Antiasthmatic; Anti-HIV; Hepatotropic; Osteopathic; Antibacterial; Vasotropic; Antiarteriosclerotic; Thrombolytic.

MECHANISM OF ACTION - P38 kinase inhibitor.

The ability of (I) to inhibit p38 kinase was tested using biological assays. The results showed that the median inhibitory concentration of

3-(2-chloro-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo(3,4-d)pyrimidine was 0.01 μ m).

USE - (I) are useful for the treatment of p38 mediated disorders (arthritis, Crohn's disease, irritable bowel syndrome, adult respiratory distress syndrome or chronic obstructive pulmonary disease) (claimed). (I) are useful for the treatment of Alzheimer's disease, influenza, multiple sclerosis, cancer, diabetes, systemic lupus erythematosus, skin-related conditions such as psoriasis, eczema, burns, dermatitis, keloid formation and scar tissue formation. (I) are also useful for the treatment of gastrointestinal conditions such as inflammatory bowel disease, gastritis and ulcerative colitis; ophthalmic diseases; angiogenesis; metastasis; diabetic retinopathy; non-malignant conditions such as infantile hemangiomas; diabetic nephropathy and cardiomyopathy; disorders of the female reproductive system such as endometriosis; pain; hepatitis C virus; severe asthma; AIDS; pneumonia and herpes virus; bone resorption diseases, endotoxic shock, reperfusion injury, autoimmune disease such as graft vs. host reaction and allograft rejections; cardiovascular diseases such as atherosclerosis, thrombosis, congestive heart failure, cardiac reperfusion injury, renal reperfusion injury, liver disease or nephritis.
Dwg.0/0

(OTW) 2004-10-10 10:10:10

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=> file hcaplus
FILE 'HCAPLUS' ENTERED AT 14:44:59 ON 19 JUL 2006
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SEARCH

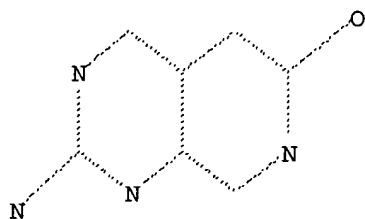
FILE COVERS 1907 - 19 Jul 2006 VOL 145 ISS 4
FILE LAST UPDATED: 18 Jul 2006 (20060718/ED)

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This file contains CAS Registry Numbers for easy and accurate substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> d stat que L6
L3 STR



Structure attributes must be viewed using STN Express query preparation.

L5 7 SEA FILE=REGISTRY SSS FUL L3
L6 2 SEA FILE=HCAPLUS ABB=ON PLU=ON L5

=> s L6 not L45
L49 1 L6 NOT (L45) → printed with author search

=> file wpix
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FILE LAST UPDATED: 14 JUL 2006 <20060714/UP>
MOST RECENT DERWENT UPDATE: 200645 <200645/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
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>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
<http://scientific.thomson.com/support/patents/coverage/latestupdates/>

>>> PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE
http://www.stn-international.de/stndatabases/details/ipc_reform.html and
<http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf> <<<

>>> FOR FURTHER DETAILS ON THE FORTHCOMING DERWENT WORLD PATENTS
INDEX ENHANCEMENTS PLEASE VISIT:
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<
'BIX' IS DEFAULT SEARCH FIELD FOR 'WPIX' FILE

=> d stat que L30

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L50 0 L30 NOT L46

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=> file marpat

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FILE CONTENT: 1961-PRESENT VOL 145 ISS 1 (20060714/ED)

SOME MARPAT RECORDS ARE DERIVED FROM INPI DATA FOR 1961-1987

MOST RECENT CITATIONS FOR PATENTS FROM MAJOR ISSUING AGENCIES
(COVERAGE TO THESE DATES IS NOT COMPLETE):

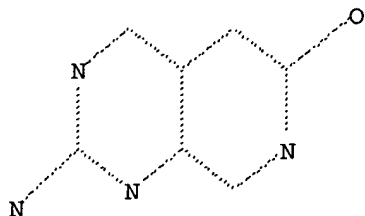
| | | |
|----|--------------|-------------|
| US | 2006118302 | 08 JUN 2006 |
| DE | 102004053653 | 04 MAY 2006 |
| EP | 1653548 | 03 MAY 2006 |
| JP | 2006112980 | 27 APR 2006 |
| WO | 2006053912 | 26 MAY 2006 |
| GB | 2419594 | 03 MAY 2006 |
| FR | 2877004 | 28 APR 2006 |
| RU | 2275374 | 27 APR 2006 |
| CA | 2518664 | 10 MAR 2006 |

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=> d stat que L21

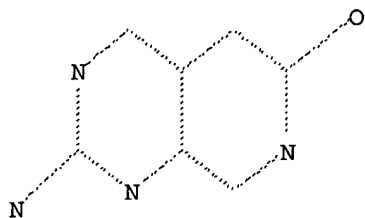
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L19 STR



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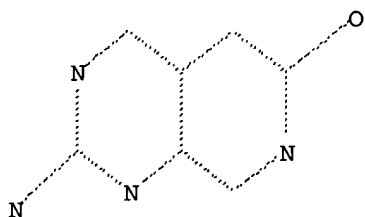
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13 ANSWERS

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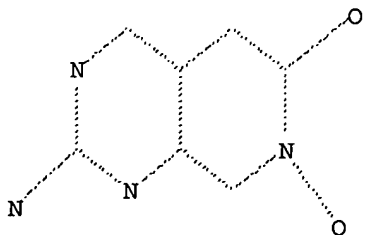
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L22 STR



Structure attributes must be viewed using STN Express query preparation.
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100.0% PROCESSED 18 ITERATIONS 2 ANSWERS
SEARCH TIME: 00.00.01

=> s (L21 or L24) not L39

L51 13 (L21 OR L24) NOT L39 → printed with author search

=> file beilstein

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FILE COVERS 1771 TO 2006.

*** FILE CONTAINS 9,606,495 SUBSTANCES ***

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separate documents and can not be searched together in one query.
Reaction data for BEILSTEIN compounds may be displayed
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information by combining with PRE/FA, REA/FA or more generally
with RX/FA. The BEILSTEIN Registry Number (BRN) is the link
between a BEILSTEIN compound and belonging reactions. For mo
detailed reaction searches BRNs can be searched as reaction
partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE <<<

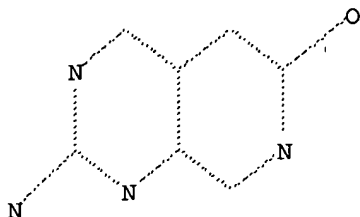
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* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE *
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COMPOUND AT A GLANCE.

=> d stat que L8

L3 STR



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100.0% PROCESSED      243 ITERATIONS                      0 ANSWERS
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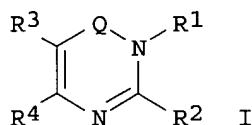
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L52 ANSWER 1 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:857326 HCAPLUS
DOCUMENT NUMBER: 141:309639
TITLE: Dipeptidyl peptidase inhibitors
INVENTOR(S): Feng, Jun; Gwaltney, Stephen L.; Kaldor, Stephen W.;
Stafford, Jeffrey A.; Wallace, Michael B.; Zhang,
Zhiyuan
PATENT ASSIGNEE(S): Syrrx, Inc., USA
SOURCE: PCT Int. Appl., 244 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|------|------|-----------------|------|
|------------|------|------|-----------------|------|

 WO 2004087053 A2 20041014 WO 2004-US9217 20040324
 WO 2004087053 C2 20041111
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 GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
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 NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
 TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
 RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
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 ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
 SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,
 TD, TG
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 US 2004242568 A1 20041202 US 2004-809636 20040324
 US 2004242566 A1 20041202 US 2004-809638 20040324
 US 2004259870 A1 20041223 US 2004-809637 20040324
 US 2005004117 A1 20050106 US 2004-809635 20040324
 EP 1608317 A2 20051228 EP 2004-758366 20040324
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK
 PRIORITY APPLN. INFO.: US 2003-457785P P 20030325
 WO 2004-US9217 W 20040324

OTHER SOURCE(S): MARPAT 141:309639
 GI



AB Dipeptidyl peptidase IV inhibitors I [Q = CO, SO, SO₂, C:NR₅; R₁ = ZR₆; Z = moiety providing 1-6 atom separation between R₆ and ring; R₂ = (substituted)3-7-membered ring; R₃,R₄ = taken together form a (substituted)5-6-membered ring; R₅ = H, (substituted)alkyl, cycloalkyl, etc.; R₆ = (substituted)C₃-7-cycloalkyl or aryl] are disclosed. Thus, 2-[2-(3-aminopiperidin-1-yl)-6,7-dimethoxy-4-oxo-4H-quinazolin-3-ylmethyl]benzonitrile (I; R₁ = 2-cyanophenylmethyl; R₂ = 3-aminopiperidin-1-yl; R₃,R₄ = dimethoxyphenyl) was synthesized. This compound exhibited enhanced stability in rat liver microsomes.

IC ICM A61K
 CC 7-3 (Enzymes)

IT 22126-97-2P 80096-35-1P 769157-54-2P 769157-55-3P 769157-56-4P
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 769158-05-6P 769158-06-7P 769158-14-7P
 RL: BSU (Biological study, unclassified); SPN (Synthetic preparation);
 BIOL (Biological study); PREP (Preparation)

(dipeptidyl peptidase inhibitors)

IT 769157-67-7P

RL: BSU (Biological study, unclassified); SPN (Synthetic preparation);

BIOL (Biological study); PREP (Preparation)

(dipeptidyl peptidase inhibitors)

RN 769157-67-7 HCAPLUS

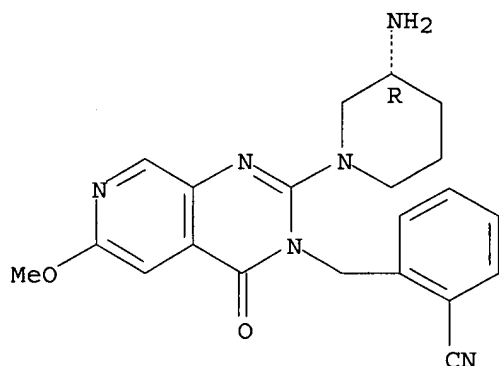
CN Benzonitrile, 2-[[2-[(3R)-3-amino-1-piperidinyl]-6-methoxy-4-oxopyrido[3,4-d]pyrimidin-3(4H)-yl]methyl]-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

CRN 769157-66-6

CMF C21 H22 N6 O2

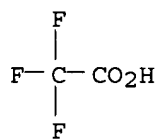
Absolute stereochemistry.



CM 2

CRN 76-05-1

CMF C2 H F3 O2



L52 ANSWER 2 OF 14 MARPAT COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 142:455888 MARPAT

TITLE: Halogenated coordination compounds preparation and use thereof

INVENTOR(S): Schwaiger, Jochen; Bach, Ingrid; Stoessel, Philipp

PATENT ASSIGNEE(S): Covion Organic Semiconductors G.m.b.H., Germany

SOURCE: PCT Int. Appl., 23 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

110

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------|----------|-----------------|----------|
| WO 2005042545 | A2 | 20050512 | WO 2004-EP11891 | 20041021 |
| WO 2005042545 | A3 | 20060105 | | |

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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

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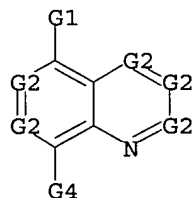
PRIORITY APPLN. INFO.:

DE 2003-10351556 20031103

OTHER SOURCE(S): CASREACT 142:455888

AB The invention relates to novel halogenated coordination compds. containing azanaphthalenols/thiols/selenols, of application as functional materials in differing applications within the widest sense of the electronic industry and which comprise organically-bonded halides as reactive groups. The invention further relates to a method for regioselective preparation of said compds. For example, AlL2 (HL = 8-hydroxyquinoline) was brominated with N-bromosuccinimide to give AlL13 (HL1 = 5-bromo-8-hydroxyquinoline) in 99 % yield.

MSTR 1

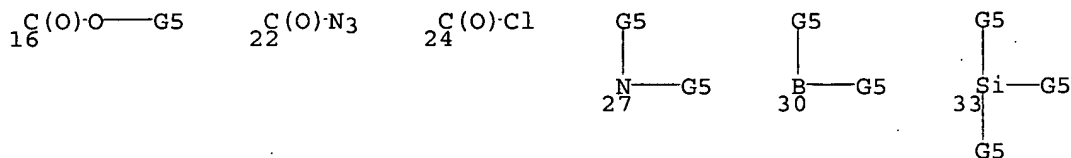


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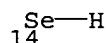
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 G2 = N / 12

C—G3
 12

G3 = H / F / Cl / Br / I / CN / CHO / 16 / 22 / 24 /
 NO2 / 27 / 30 / 33 / carbon chain <containing 1 or more C>
 (opt. substd.) / 36



G4 = OH / SH / 14 / aryl <containing up to 40 C>
 (opt. substd.) / heteroaryl <containing up to 40 atoms,
 zero or more O, zero or more S,
 zero or more N (no other heteroatoms)> (opt. substd.)



G5 = H / R

G6 = carbon chain <containing 1 or more C>
 (opt. substd.) / aryl <containing up to 40 C>
 (opt. substd.) / heteroaryl <containing up to 40 atoms,
 zero or more O, zero or more S,
 zero or more N (no other heteroatoms)> (opt. substd.)

G10 = R <"metal"> / (Specifically claimed: Al / Be / B /
 Ca / Ga / In / Ir / Li / Mg / Zn)

Patent location: claim 1

Note: as complexes with G10

Note: additional ligands and ring formation also claimed

Note: also incorporates claim 13, structure IV

L52 ANSWER 3 OF 14 MARPAT COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 142:463438 MARPAT

TITLE: Preparation of phenylamine substituted bicyclic
 heterocyclic compounds useful as kinase inhibitors

INVENTOR(S): Das, Jagabandhu; Hynes, John; Leftheris, Katerina;
 Lin, Shuqun; Wroblewski, Stephen T.; Wu, Hong

PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA

SOURCE: PCT Int. Appl., 113 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

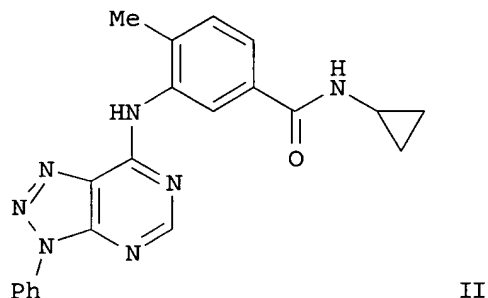
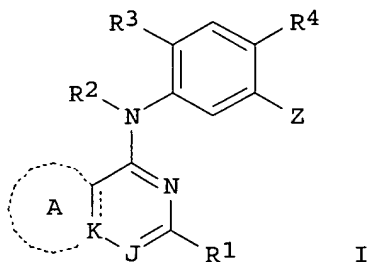
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2005042537 | A1 | 20050512 | WO 2004-US35116 | 20041022 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US,*UZ, VC, VN, YU, ZA, ZM, ZW | | | | |

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
 AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
 EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
 SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
 SN, TD, TG

US 2005143398 A1 20050630
 PRIORITY APPLN. INFO.:
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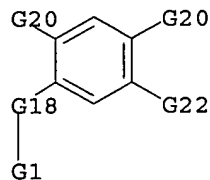
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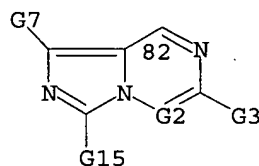
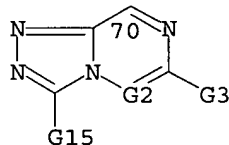
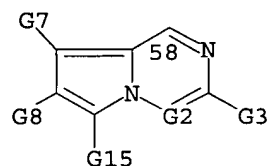
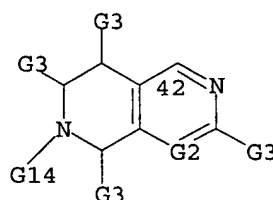
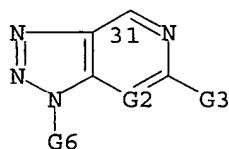
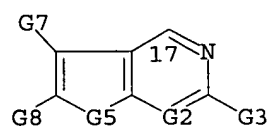
AB Title compds. I [J = N or CR5; R1 and R5 independently = H, OH, halo, CN, etc.; R2 = H or alkyl; R3 and R4 independently = H, (un)substituted-alkyl, OH, MeO, halo, etc.; K = N or C; Z = NHR6, CONR6R7, NR6CO2R7, etc.; R6 = H or (un)substituted alkyl; R7 = H, OH, alkoxy, etc.; Ring A = fused heterocycle or carbocycle], and their pharmaceutically acceptable salts, prodrugs, and solvates thereof, are prepared and disclosed as kinase inhibitors. Thus, e.g., II was prepared by reaction of 4-chloro-1-phenyl-1,2,3,5,7-azaindene with 3-amino-4-methyl-N-cyclopropylbenzamide. I have shown activity as inhibitors of p38 α / β enzymes and TNF- α (no data).

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

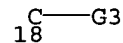
MSTR 1



G1 = 17 / 31 / 42 / 58 / 70 / 82



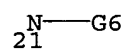
G2 = N / 18



G3 = H / alkyl <containing 1-12 C> (opt. substd.) / OH /
alkoxy <containing 1-12 C> / F / Cl / Br / I / CN / NH2 /
alkylamino <containing 1-12 C> (opt. substd.) /
dialkylamino <each alkyl containing 1-12 C> (opt. substd.) /
alkoxy <containing 1-12 C> (substd. by 1 or more G4) /
carbocycle <0 or more double bonds> (opt. substd.) /
aryl (opt. substd.) / heterocycle <containing zero or more
N, zero or more O, zero or more S, non-aromatic,
0 or more double bonds> (opt. substd.) /
heteroaryl <containing zero or more N, zero or more O,
zero or more S> (opt. substd.)

G4 = F / Cl / Br / I

G5 = 21 / S

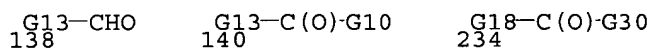
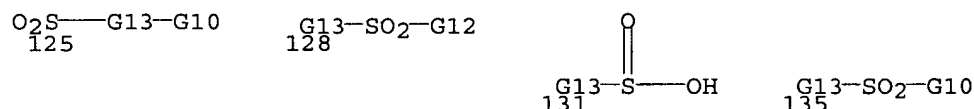
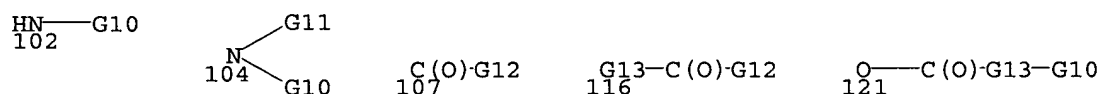
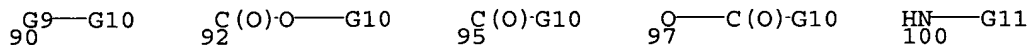


G6 = alkyl <containing 1-12 C> (opt. substd.) /
aryl (opt. substd.) / heteroaryl <containing zero or more N,
zero or more O, zero or more S> (opt. substd.) /
(Specifically claimed: Ph (opt. substd.))

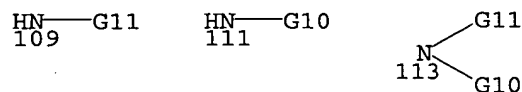
G7 = H / Me / CF3 / OMe / F / Cl / Br / I / CN / NH2 /
NHMe

G8 = H / carbon chain <containing 1-12 C>

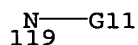
(opt. substd.) / aryl (opt. substd.) /
heteroaryl <containing zero or more N, zero or more O,
zero or more S> (opt. substd.) /
heterocycle <containing zero or more N, zero or more O,
zero or more S, non-aromatic, 0 or more double bonds>
(opt. substd.) / carbocycle <0 or more double bonds>
(opt. substd.) / F / Cl / Br / I / CN / NO₂ / OH / SH / 90 /
CO₂H / 92 / CHO / 95 / OCHO / 97 / NH₂ / 100 / 102 / 104 /
107 / 116 / 121 / 125 / 128 / 131 / 135 / 138 / 140 /
(Specifically claimed: 234)



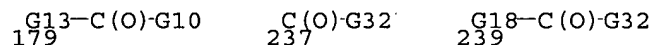
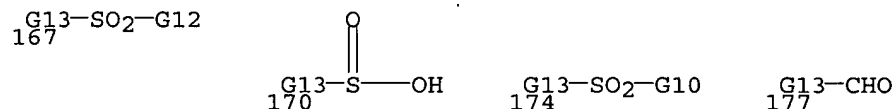
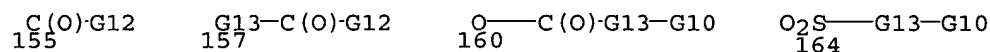
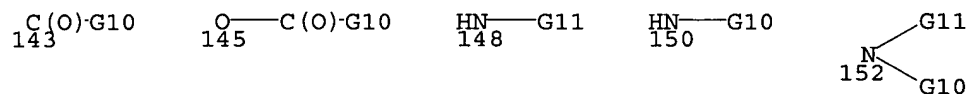
G9 = O / S / S(O) / SO₂
G10 = carbon chain <containing 1-12 C> (opt. substd.) /
aryl (opt. substd.) / heteroaryl <containing zero or more N,
zero or more O, zero or more S> (opt. substd.) /
heterocycle <containing zero or more N, zero or more O,
zero or more S, non-aromatic, 0 or more double bonds>
(opt. substd.) / carbocycle <0 or more double bonds>
(opt. substd.)
G11 = alkyl <containing 1-12 C> (opt. substd.) /
aryl (opt. substd.) / carbocycle <0 or more double bonds>
(opt. substd.) / heterocycle <containing zero or more N,
zero or more O, zero or more S, non-aromatic,
0 or more double bonds> (opt. substd.) /
heteroaryl <containing zero or more N, zero or more O,
zero or more S> (opt. substd.)
G12 = NH₂ / 109 / 111 / 113



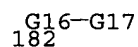
G13 = NH / 119



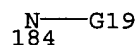
G14 = H / NO₂ / CHO / 143 / OCHO / 145 / NH₂ / 148 / 150 / 152 / 155 / 157 / 160 / 164 / 167 / 170 / 174 / 177 / 179 / carbon chain <containing 1-12 C> (opt. substd.) / aryl (opt. substd.) / heteroaryl <containing zero or more N, zero or more O, zero or more S> (opt. substd.) / heterocycle <containing zero or more N, zero or more O, zero or more S, non-aromatic, 0 or more double bonds> (opt. substd.) / carbocycle <0 or more double bonds> (opt. substd.) / (Specifically claimed: 237 / 239)



G15 = H / alkyl <containing 1-12 C> (opt. substd.) / F / Cl / Br / I / CN / aryl (opt. substd.) / heteroaryl <containing zero or more N, zero or more O, zero or more S> (opt. substd.) / 182 / (Specifically claimed: Ph)

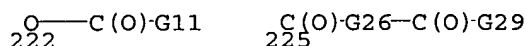
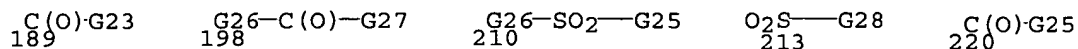


G16 = S / SO₂
 G17 = alkyl <containing 1-12 C> (opt. substd.)
 G18 = NH / 184

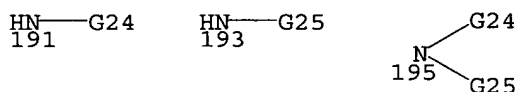


G19 = alkyl <containing 1-4 C>
 G20 = H / alkyl <containing 1-4 C> (opt. substd. by (1-2) G21) / OH / OMe / F / Cl / Br / I / CN / NH₂ / alkylamino <containing 1-4 C> / dialkylamino <each alkyl containing 1-4 C> / CF₃ / OCF₃ / (Specifically claimed: Me)
 G21 = OH / OMe / F / Cl / Br / I / CN / NH₂ / alkylamino <containing 1-4 C> / dialkylamino <each alkyl containing 1-4 C> / CF₃ / OCF₃

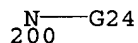
G22 = NH2 / alkylamino <containing 1-12 C>
 (opt. substd.) / 189 / 198 / 210 / 213 / CHO / 220 / OCHO /
 222 / 225 / heteroaryl <containing zero or more N,
 zero or more O, zero or more S> (opt. substd.)



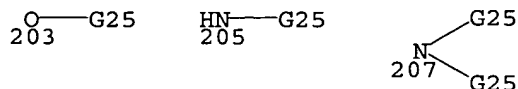
G23 = NH2 / 191 / 193 / 195



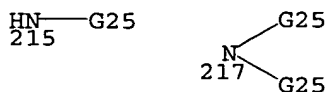
G24 = alkyl <containing 1-12 C> (opt. substd.)
 G25 = alkyl <containing 1-12 C> (opt. substd.) /
 alkenyl <containing 2-20 C, up to 4 double bonds>
 (opt. substd.) / OH / alkoxy <containing 1-12 C> /
 aryl (opt. substd.) / carbocycle <0 or more double bonds>
 (opt. substd.) / heteroaryl <containing zero or more N,
 zero or more O, zero or more S> (opt. substd.) /
 heterocycle <containing zero or more N, zero or more O,
 zero or more S, non-aromatic, 0 or more double bonds>
 (opt. substd.) / (Specifically claimed: cyclopropyl /
 pyrazolyl / oxazolyl / isoxazolyl / Ph / pyridyl)
 G26 = NH / 200



G27 = OH / 203 / H / alkyl <containing 1-12 C>
 (opt. substd.) / alkenyl <containing 2-20 C,
 up to 4 double bonds> (opt. substd.) / OH /
 alkoxy <containing 1-12 C> / aryl (opt. substd.) /
 carbocycle <0 or more double bonds> (opt. substd.) /
 heteroaryl <containing zero or more N, zero or more O,
 zero or more S> (opt. substd.) /
 heterocycle <containing zero or more N, zero or more O,
 zero or more S, non-aromatic, 0 or more double bonds>
 (opt. substd.) / NH2 / 205 / 207

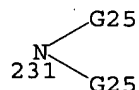


G28 = NH2 / 215 / 217



G29 = H / alkyl <containing 1-12 C> (opt. substd.) /
 alkenyl <containing 2-20 C, up to 4 double bonds>
 (opt. substd.) / OH / alkoxy <containing 1-12 C> /
 aryl (opt. substd.) / carbocycle <0 or more double bonds>
 (opt. substd.) / heteroaryl <containing zero or more N,
 zero or more O, zero or more S> (opt. substd.) /
 heterocycle <containing zero or more N, zero or more O,
 zero or more S, non-aromatic, 0 or more double bonds>
 (opt. substd.) / NH2 / 229 / 231

HN—G25
 229



G30 = H / alkyl <containing 1-6 C> /
 alkoxy <containing 1-6 C> / carbocycle <containing 3-7 C> /
 morpholino / alkyl <containing 1-4 C>
 (substd. by 1 or more G31) / (Specifically claimed: CH2Ph)

G31 = Ph / pyridyl

G32 = alkyl <containing 1-6 C>
 (opt. substd. by 1 or more G33) / imidazolyl / pyrazolyl /
 pyridyl / Ph / morpholino

G33 = Ph / morpholino

Patent location: claim 1

Note: substitution is restricted

Note: additional substitution also claimed

Note: and pharmaceutically acceptable salts, prodrugs,
 and solvates

Stereochemistry: and enantiomers or diastereomers

L52 ANSWER 4 OF 14 MARPAT COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 144:36332 MARPAT

TITLE: Preparation of tri-and bi-cyclic heteroaryl
 histamine-3 receptor ligands

INVENTOR(S): Altenbach, Robert J.; Black, Lawrence A.; Chang,
 Sou-Jen; Cowart, Marlon D.; Faghieh, Ramin; Gfesser,
 Gregory A.; Ku, Yi-Yin; Liu, Huaqing; Lukin, Kirill
 A.; Nersesian, Diana L.; Pu, Yu-Ming; Curtis, Michael
 P.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 40 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

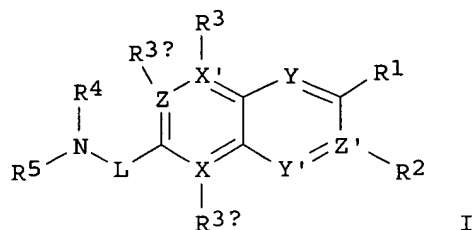
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

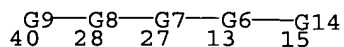
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|------------------------|------|----------|-----------------|----------|
| US 2005272736 | A1 | 20051208 | US 2005-123324 | 20050506 |
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GI

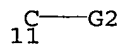


AB Title compds. I [Y and Y' independently = CH, CF, and N; X, X', Z and W independently = C or N; one of R1 and R2 is selected from L2R6 with the other of R1 and R2 = H, alkyl, alkoxy, etc.; L2 = O, CO, S, NH, etc.; R6 = bicyclic or tricyclic ring, each containing at least two heteroatoms; R3 = H, alkyl, alkoxy, halo, etc., or R3 is absent when X' = N; R3a = H, Me, alkoxy, halo, etc., or R3a is absent when Z = N; R3b = H, OH, alkyl, alkoxy, etc., or R3b is absent when X = N; R4 and R5 independently = alkyl, haloalkyl, hydroxyalkyl, etc.; or R4 and R5 taken together to form heterocyclic ring], and their pharmaceutically acceptable salts, are prepared and disclosed as useful in treating conditions or disorders prevented by or ameliorated by histamine-3 receptor ligands. Also disclosed are pharmaceutical compns. comprising the histamine-3 receptor ligands, methods for using such compds. and compns., and a process for preparing I. Thus, e.g., 6-[2-((2R)-2-methylpyrrolidin-1-yl)ethyl]-2-(4H-thieno[3,2-b]pyrrol-5-yl)quinoline was prepared via a multistep synthesis from (S)-Toluene-4-sulfonic acid 5-oxopyrrolidin-2-ylmethyl ester. In histamine-3 receptor binding studies, I demonstrated binding affinities from 810 nM to 0.02 nM.

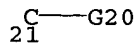
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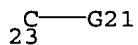
G1 = N / 11



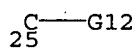
G2 = H / F
G3 = N / 21



G4 = N / 23



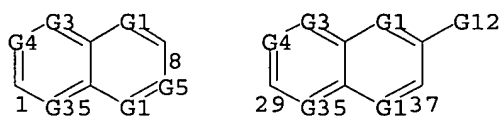
G5 = N / 25



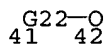
G6 = O / C(O) / S / alkylene <containing 1-4 C,
unbranched> (opt. substd. by 1 or more G15) / G16 / **NH** / 16
/ 18-27 19-15



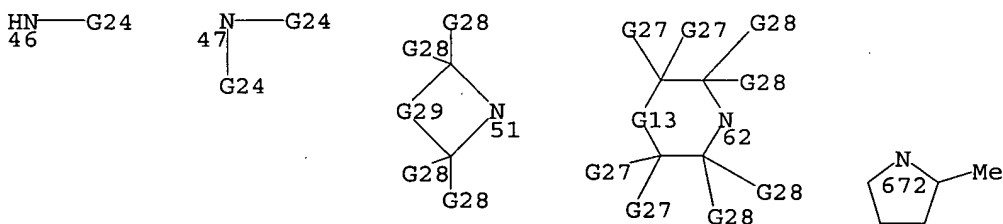
G7 = 1-28 8-13 / 29-28 37-13



G8 = alkylene <containing 1-6 C>
(opt. substd. by 1 or more G10) / G11 / 41-40 42-27



G9 = NH2 / 46 / 47 / heterocycle <containing 5-13 atoms,
1-3 heteroatoms, 1 or more N, zero or more O,
zero or more S (no other heteroatoms),
attached through 1 or more N, non-aromatic,
0 or more double bonds, mono- or bicyclic>
(opt. substd. by 1 or more G26) / 51 / 62 /
(Specifically claimed: 672)

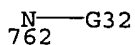


G10 = alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F

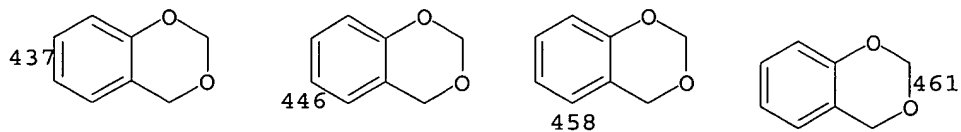
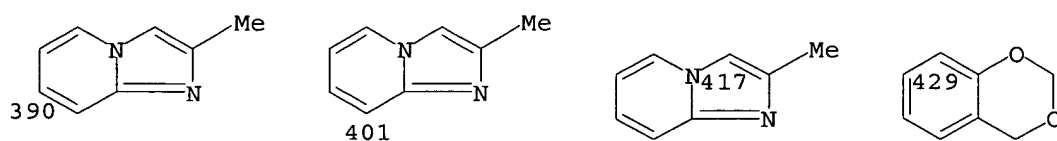
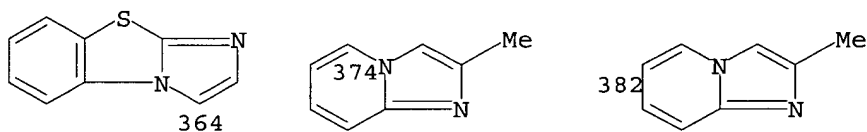
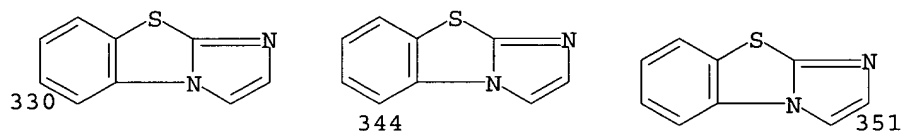
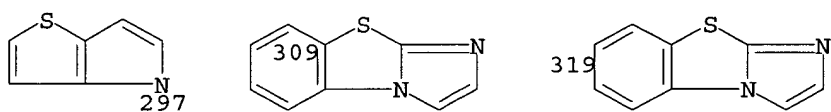
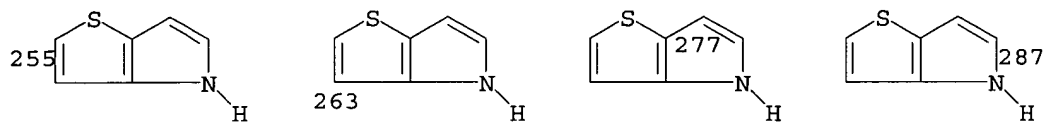
G11 = (1-6) CH2

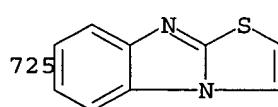
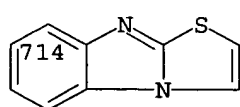
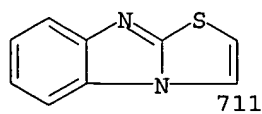
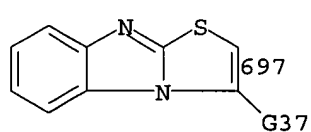
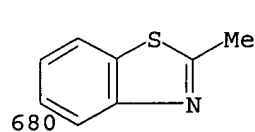
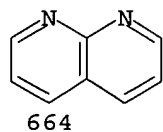
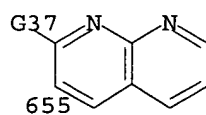
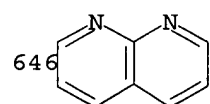
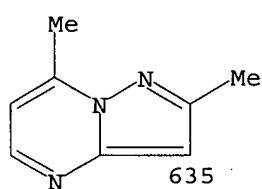
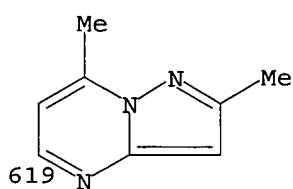
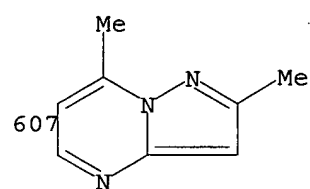
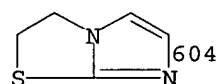
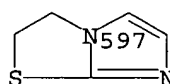
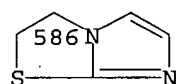
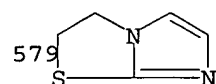
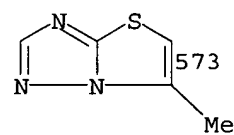
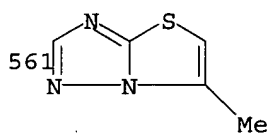
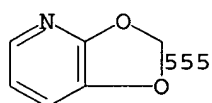
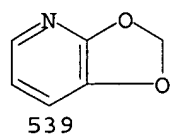
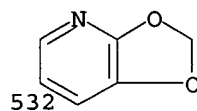
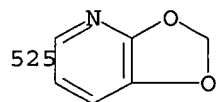
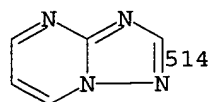
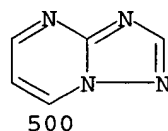
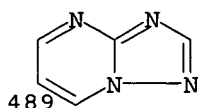
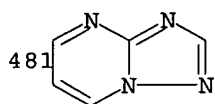
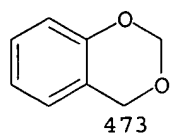
G12 = H / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / aryl (opt. substd.) /
cycloalkyl <containing 3-8 C> / F / Cl / Br / I / CN /
alkylthio <containing 1-10 C>

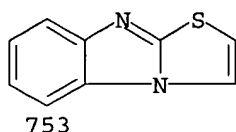
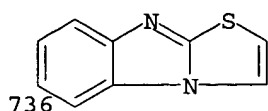
G13 = O / S / 762 / bond



G14 = heterocycle <containing 2 or more heteroatoms,
 zero or more N, zero or more O, zero or more S, 2-3 rings> /
 (Specifically claimed: 255 / 263 / 277 / 287 / 297 / 309 /
 319 / 330 / 344 / 351 / 364 / 374 / 382 / 390 / 401 / 417 /
 429 / 437 / 446 / 458 / 461 / 473 / 481 / 489 / 500 / 514 /
 benzothiazolyl / benzotriazolyl / 525 / 532 / 539 / 555 /
 561 / 573 / 579 / 586 / 597 / 604 / 607 / 619 / 635 / 646 /
 655 / 664 / quinoxalinyll / 680 / 697 / 711 / 714 / 725 /
 736 / 753)







- G15 = OH / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F
- G16 = (1-4) CH₂
- G17 = alkyl <containing 1-10 C>
- G19 = alkylene <containing 1-4 C, unbranched>
(opt. substd. by 1 or more G15) / G16
- G20 = H / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F / Cl / Br / I / CN /
alkylthio <containing 1-10 C>
- G21 = H / Me / alkoxy <containing 1-10 C> / F / Cl / Br /
I / CN
- G22 = alkylene <containing 2-6 C>
(opt. substd. by 1 or more G10) / G23
- G23 = (2-6) CH₂
- G24 = alkyl <containing 1-10 C>
(opt. substd. by 1 or more G25) /
cycloalkyl <containing 3-8 C>
- G25 = F / Cl / Br / I / OH / alkoxy <containing 1-10 C> /
cycloalkyl <containing 3-8 C> / NH₂ (opt. substd.)
- G26 = H / alkyl <containing 1-10 C> (substd. by OH) /
alkyl <containing 1-10 C> (substd. by 1 or more F) / OH /
alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> /
alkylamino <containing 1-10 C> /
dialkylamino <each alkyl containing 1-10 C> / F /
alkyl <containing 1-10 C> / alkylcarbonyl <containing 1-10 C>
/ CONH₂ / CHO / alkylaminocarbonyl <containing 1-10 C> /
dialkylaminocarbonyl <each alkyl containing 1-10 C>
- G27 = H / OH / alkyl <containing 1-10 C>
(opt. substd. by OH) / F
- G28 = H / alkyl <containing 1-10 C> (opt. substd. by OH) /
alkyl <containing 1-10 C> (substd. by 1 or more F)
- G29 = (1-5) 57

G30- $\overset{57}{\text{C}}$ -G30

- G30 = H / OH / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / alkylamino <containing 1-10 C> /
dialkylamino <each alkyl containing 1-10 C> / F
- G32 = H / alkyl <containing 1-10 C> /
alkylcarbonyl <containing 1-10 C> / CONH₂ / CHO /
alkylaminocarbonyl <containing 1-10 C> /
dialkylaminocarbonyl <each alkyl containing 1-10 C>
- G35 = N / 252

$\overset{252}{\text{C}}$ -G36

- G36 = H / alkyl <containing 1-10 C> /

alkoxy <containing 1-10 C> / F / Cl / Br / I / OH / CN /
alkylthio <containing 1-10 C>

G37 = H / Me

Patent location:

claim 1

Note:

substitution is restricted

Note:

or pharmaceutically acceptable salts, esters,
amides, or prodrugs

L52 ANSWER 5 OF 14 MARPAT COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 144:36264 MARPAT

TITLE: Preparation of bicyclic amines bearing heterocyclic
substituents as H3 receptor ligands

INVENTOR(S): Altenbach, Robert J.; Black, Lawrence A.; Chang,
Sou-Jen; Cowart, Marlon D.; Faghih, Ramin; Gfesser,
Gregory A.; Ku, Yi-Yin; Liu, Huaqing; Lukin, Kirill
A.; Nersesian, Diana L.; Pu, Yu-Ming; Curtis, Michael
P.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 42 pp.

CODEN: USXXCO

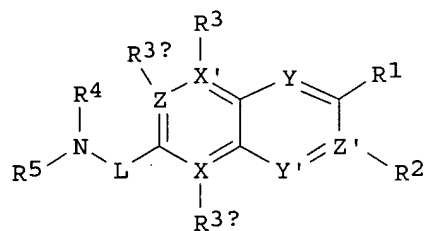
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

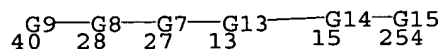
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------------|------|----------|-----------------|----------|
| US 2005272728 | A1 | 20051208 | US 2005-123620 | 20050506 |
| PRIORITY APPLN. INFO.: GI | | | US 2004-570186P | 20040512 |

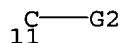


AB Title compds. I [Y, Y' = CH, CF, N; X, X', Z, Z' = C, N; R1, R2 = H, alkyl, alkoxy, aryl, cycloalkyl, etc.; R3 = absent when X' is N or H, alkyl, alkoxy, etc.; R3 = absent when X' is N or R3 = H, alkyl, alkoxy, halo, etc.; R3a = absent when Z is N or R3a = H, Me, alkoxy, halo, CN; R3b = absent when X is N or R3b = H, alkyl, alkoxy, halo, etc.; R4-5 = alkyl, haloalkyl, hydroxyalkyl, etc.; L = divalent alkyl, etc.] are prepared For instance, 6-[2-((2R)-2-methylpyrrolidin-1-yl)ethyl]-2-(4-methyl-2-thien-2-yl-1,3-thiazol-5-yl)quinoline is prepared in 7 steps from (S)-(5-oxopyrrolidin-2-yl)methyl 4-methylbenzenesulfonate, 1-(2-bromoethyl)-4-nitrobenzene, trimethylacetyl chloride, DMF and 1-(4-methyl-2-(thiophene-2-yl)thiazol-5-yl)ethanone. Representative compds. of the invention demonstrated binding affinities for the H3 receptor from about 810 nM to about 0.02 nM. I are useful for the treatment of conditions or disorders prevented by or ameliorated by histamine-3 receptor ligands. Also disclosed are pharmaceutical compns.

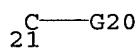
comprising the histamine-3 receptor ligands, methods for using such compds. and compns., and a process for preparing I.

MSTR 1A

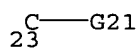
G1 = N / 11



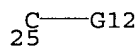
G2 = H / F
G3 = N / 21



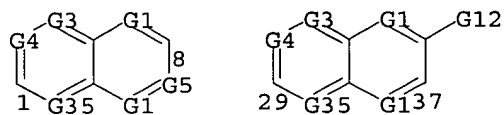
G4 = N / 23



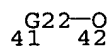
G5 = N / 25



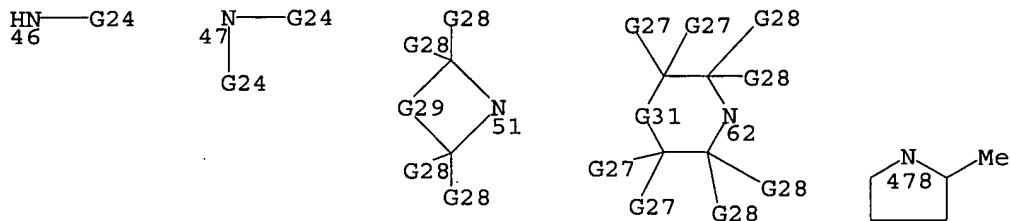
G7 = 1-28 8-13 / 29-28 37-13



G8 = alkylene <containing 1-6 C>
(opt. substd. by 1 or more G10) / G11 / 41-40 42-27



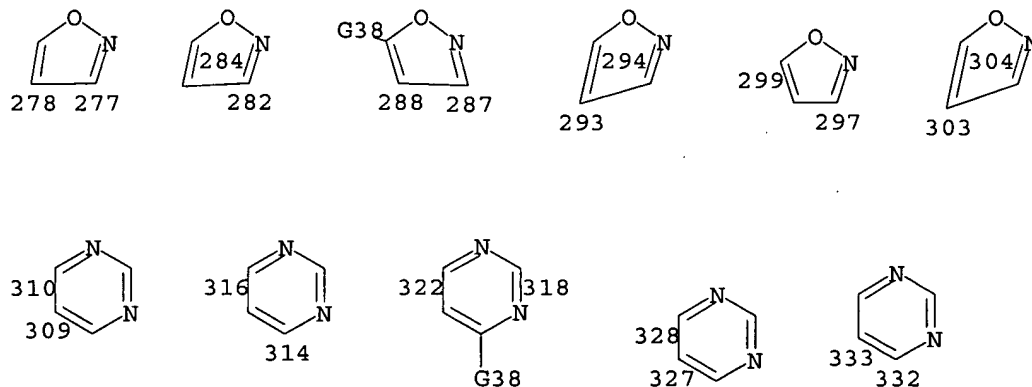
G9 = NH2 / 46 / 47 / heterocycle <containing 5-13 atoms,
1-3 heteroatoms, 1 or more N, zero or more O,
zero or more S (no other heteroatoms),
attached through 1 or more N, non-aromatic,
0 or more double bonds, mono- or bicyclic>
(opt. substd. by 1 or more G26) / 51 / 62 /
(Specifically claimed: 478)

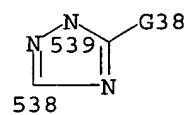
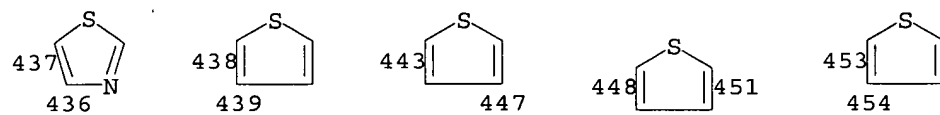
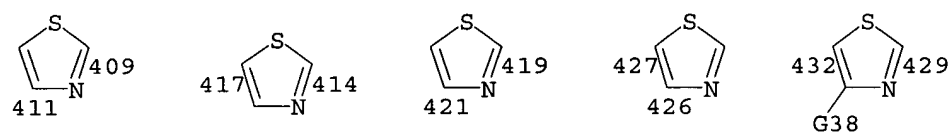
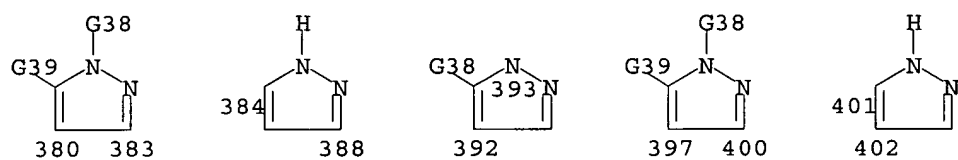
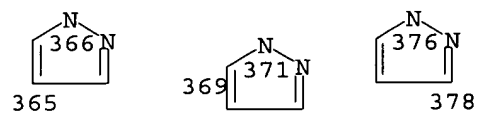
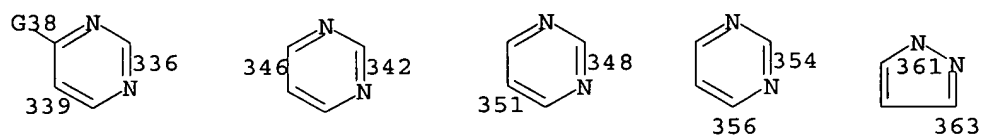


- G10 = alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F
G11 = (1-6) CH₂
G12 = H / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / aryl (opt. substd.) /
cycloalkyl <containing 3-8 C> / F / Cl / Br / I / CN /
alkylthio <containing 1-10 C> / (Specifically claimed: Me)
G13 = O / C(O) / S / alkylene <containing 1-4 C,
unbranched> (opt. substd.) / NH / 16 / 18-27 19-15



- G14 = any ring <containing 5-8 atoms, zero or more N,
zero or more O, zero or more S> /
(Specifically claimed: phenylene / 277-13 278-254 /
282-13 284-254 / 288-13 287-254 / 293-13 294-254 /
299-13 297-254 / 304-13 303-254 / 310-13 309-254 /
316-13 314-254 / 322-13 318-254 / 327-13 328-254 /
333-13 332-254 / 339-13 336-254 / 342-13 346-254 /
348-13 351-254 / 354-13 356-254 / 361-13 363-254 /
366-13 365-254 / 371-13 369-254 / 378-13 376-254 /
383-13 380-254 / 388-13 384-254 / 392-13 393-254 /
397-13 400-254 / 402-13 401-254 / 409-13 411-254 /
414-13 417-254 / 421-13 419-254 / 426-13 427-254 /
432-13 429-254 / 437-13 436-254 / 438-13 439-254 /
443-13 447-254 / 448-13 451-254 / 454-13 453-254 /
459-13 462-254 / 464-13 466-254 / 468 / 473-13 475-254 /
heterocycle <containing 5 atoms, 3 N, 2 C, aromatic,
2 double bonds, 5-membered monocyclic ring> /
532-13 533-254 / 538-13 539-254)





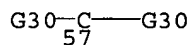
G15 = G37 / 255

$\frac{G16-G37}{255 \ 256}$

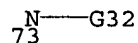
G16 = R <"linking group"> / (Specifically claimed: 271-15
272-256 / 273-15 274-256)



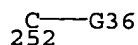
G17 = alkyl <containing 1-10 C>
G19 = alkylene <containing 1-4 C, unbranched>
(opt. substd.)
G20 = H / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F / Cl / Br / I / CN /
alkylthio <containing 1-10 C>
G21 = H / Me / alkoxy <containing 1-10 C> / F / Cl / Br /
I / CN
G22 = alkylene <containing 2-6 C>
(opt. substd. by 1 or more G10) / G23
G23 = (2-6) CH2
G24 = alkyl <containing 1-10 C>
(opt. substd. by 1 or more G25) /
cycloalkyl <containing 3-8 C>
G25 = F / Cl / Br / I / OH / alkoxy <containing 1-10 C> /
cycloalkyl <containing 3-8 C> / NH2 (opt. substd.)
G26 = H / alkyl <containing 1-10 C> (substd. by OH) /
alkyl <containing 1-10 C> (substd. by 1 or more F) / OH /
alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> /
alkylamino <containing 1-10 C> /
dialkylamino <each alkyl containing 1-10 C> / F /
alkyl <containing 1-10 C> / alkylcarbonyl <containing 1-10 C>
/ CONH2 / CHO / alkylaminocarbonyl <containing 1-10 C> /
dialkylaminocarbonyl <each alkyl containing 1-10 C>
G27 = H / OH / alkyl <containing 1-10 C>
(opt. substd. by OH) / F
G28 = H / alkyl <containing 1-10 C> (opt. substd. by OH) /
alkyl <containing 1-10 C> (substd. by 1 or more F)
G29 = (1-5) 57



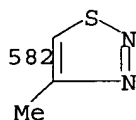
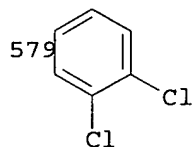
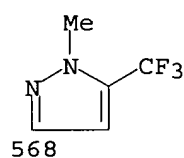
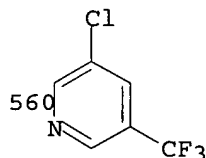
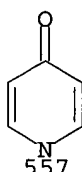
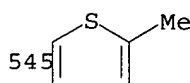
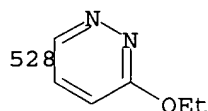
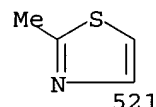
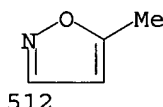
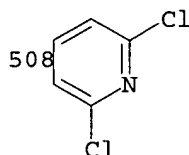
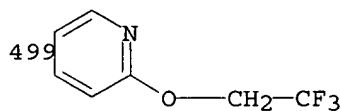
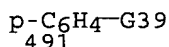
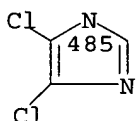
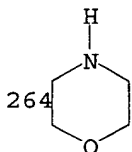
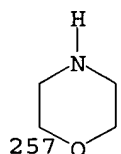
G30 = H / OH / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / alkylamino <containing 1-10 C> /
dialkylamino <each alkyl containing 1-10 C> / F
G31 = bond / O / S / 73



G32 = H / alkyl <containing 1-10 C> /
alkylcarbonyl <containing 1-10 C> / CONH2 / CHO /
alkylaminocarbonyl <containing 1-10 C> /
dialkylaminocarbonyl <each alkyl containing 1-10 C>
G35 = N / 252



- G36 = H / alkyl <containing 1-10 C> /
 alkoxy <containing 1-10 C> / F / Cl / Br / I / OH / CN /
 alkylthio <containing 1-10 C>
 G37 = any ring <containing 5-8 atoms, zero or more N,
 zero or more O, zero or more S> /
 (Specifically claimed: isoxazolyl / morpholino / 257 / 264 /
 491 / pyridazinyl / pyridyl / pyrimidinyl / pyrazinyl /
 pyrazolyl / thiadiazolyl / thiazolyl / thienyl / triazolyl /
 cyclobutyl / pyrrolidino / 485 / 499 / 508 / 512 / 521 /
 528 / 545 / piperidino / 557 / 560 / 568 / 579 / 582)



G38 = H / Me
 G39 = H / Cl
 Patent location:
 Note:
 Note:

claim 1
 substitution is restricted
 or pharmaceutically acceptable salts, esters,
 amides, or prodrugs

L52 ANSWER 6 OF 14 MARPAT COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 143:477959 MARPAT
 TITLE: Preparation of tri- and bi-cyclic heteroaryl
 histamine-3 receptor ligands

INVENTOR(S): Altenbach, Robert J.; Black, Lawrence A.; Chang, Sou-Jen; Cowart, Marlon D.; Faghih, Ramin; Gfesser, Gregory A.; Ku, Yi-Yin; Liu, Huaqing; Lukin, Kirill A.; Nersesian, Diana L.; Pu, Yu-Ming; Curtis, Michael P.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 40 pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

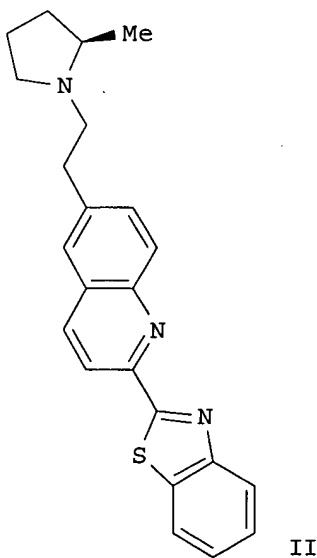
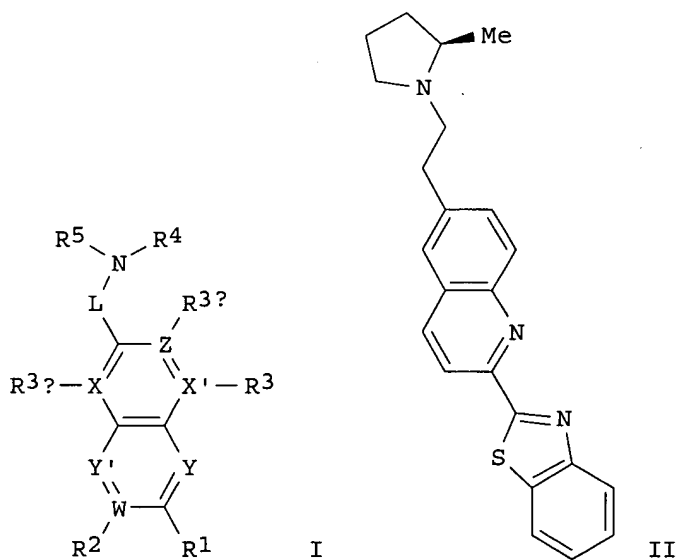
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------|----------|-----------------|----------|
| US 2005256309 | A1 | 20051117 | US 2004-844101 | 20040512 |
| WO 2005113536 | A2 | 20051201 | WO 2005-US14866 | 20050429 |
| WO 2005113536 | A3 | 20060330 | | |

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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

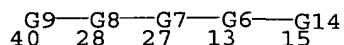
PRIORITY APPLN. INFO.:
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US 2004-844101 20040512

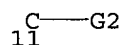


AB Title compds. I [Y and Y' independently = CH, CF, and N; X, X', Z and W independently = C or N; one of R1 and R2 is selected from L2R6 with the other of R1 and R2 = H, alkyl, alkoxy, etc.; L2 = O, CO, S, NH, etc.; R6 = bicyclic or tricyclic ring, each containing at least two heteroatoms; R3 = H, alkyl, alkoxy, halo, etc., or R3 is absent when X' = N; R3a = H, Me, alkoxy, halo, etc., or R3a is absent when Z = N; R3b = H, OH, alkyl, alkoxy, etc., or R3b is absent when X = N; R4 and R5 independently = alkyl, haloalkyl, hydroxyalkyl, etc.; or R4 and R5 taken together to form heterocyclic ring], and their pharmaceutically acceptable salts, are prepared and disclosed as useful in treating conditions or disorders prevented by or ameliorated by histamine-3 receptor ligands. Thus, e.g., II was prepared via a multistep synthesis from (S)-Toluene-4-sulfonic acid 5-oxopyrrolidin-2-ylmethyl ester. In histamine-3 receptor binding studies, I demonstrated binding affinities from 810 nM to 0.02 nM. Also disclosed are pharmaceutical compns. comprising the histamine-3 receptor ligands, methods for using such compds. and compns., and a process for preparing compds. within the scope of formula (I).

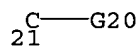
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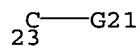
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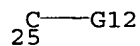
G2 = H / F
G3 = N / 21



G4 = N / 23



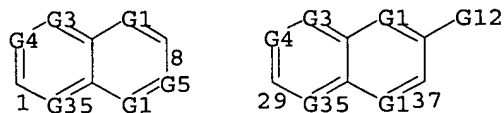
G5 = N / 25



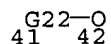
G6 = O / C(O) / S / alkylene <containing 1-4 C,
unbranched> (opt. substd. by 1 or more G15) / G16 / NH / 16
/ 18-27 19-15



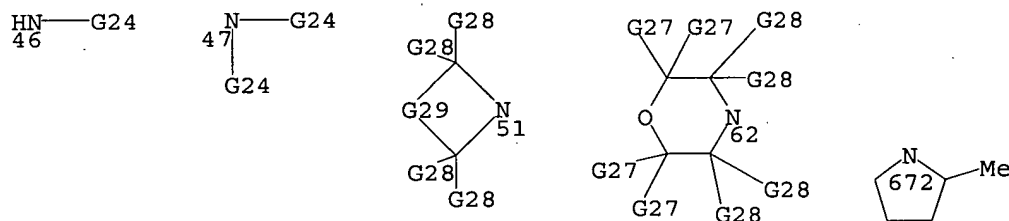
G7 = 1-28 8-13 / 29-28 37-13



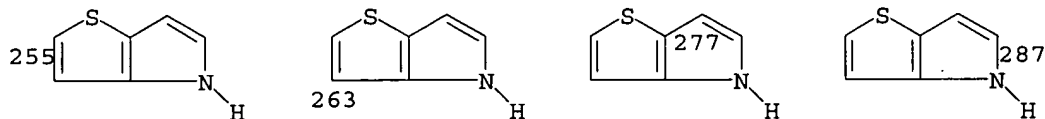
G8 = alkylene <containing 1-6 C>
(opt. substd. by 1 or more G10) / G11 / 41-40 42-27

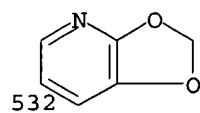
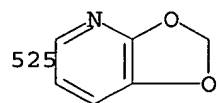
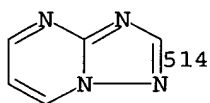
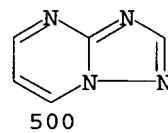
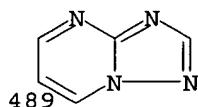
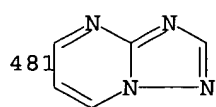
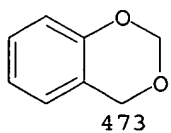
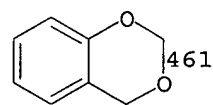
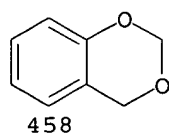
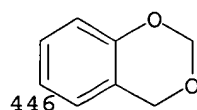
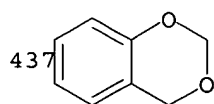
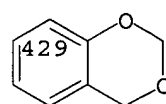
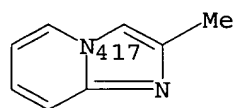
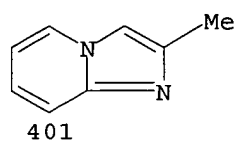
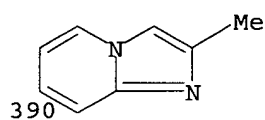
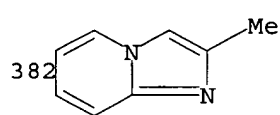
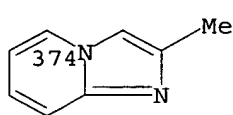
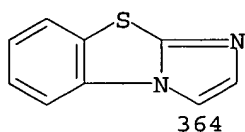
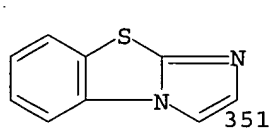
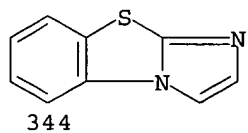
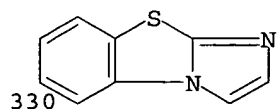
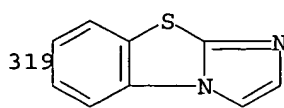
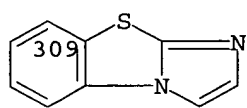
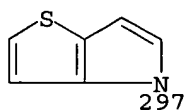


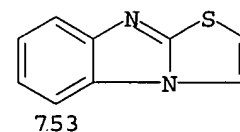
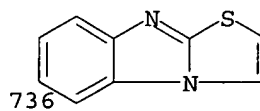
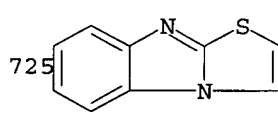
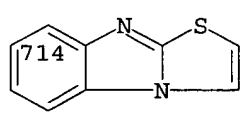
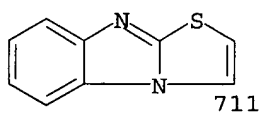
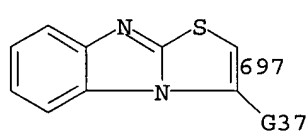
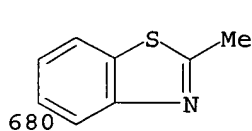
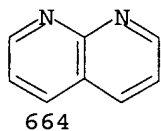
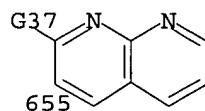
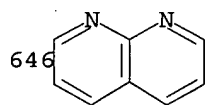
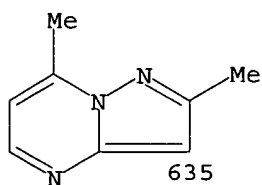
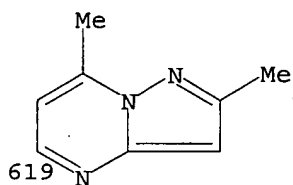
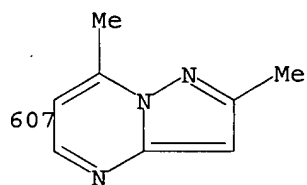
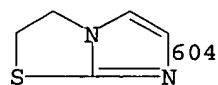
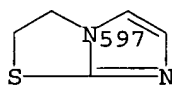
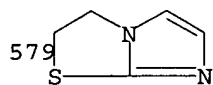
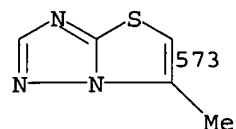
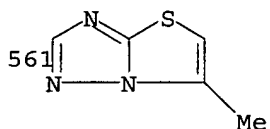
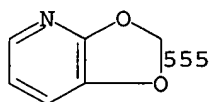
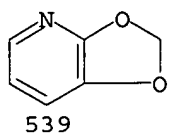
G9 = NH2 / 46 / 47 / heterocycle <containing 5-13 atoms,
1-3 heteroatoms, 1 or more N, zero or more O,
zero or more S (no other heteroatoms),
attached through 1 or more N, non-aromatic,
0 or more double bonds, mono- or bicyclic>
(opt. substd. by 1 or more G26) / 51 / 62 /
(Specifically claimed: 672)



G10 = alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F
G11 = (1-6) CH2
G12 = H / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / aryl (opt. substd.) /
cycloalkyl <containing 3-8 C> / F / Cl / Br / I / CN /
alkylthio <containing 1-10 C>
G14 = heterocycle <containing 2 or more heteroatoms,
zero or more N, zero or more O, zero or more S, 2-3 rings> /
(Specifically claimed: 255 / 263 / 277 / 287 / 297 / 309 /
319 / 330 / 344 / 351 / 364 / 374 / 382 / 390 / 401 / 417 /
429 / 437 / 446 / 458 / 461 / 473 / 481 / 489 / 500 / 514 /
benzothiazolyl / benzotriazolyl / 525 / 532 / 539 / 555 /
561 / 573 / 579 / 586 / 597 / 604 / 607 / 619 / 635 / 646 /
655 / 664 / quinoxalinyl / 680 / 697 / 711 / 714 / 725 /
736 / 753)







- G15 = OH / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F
- G16 = (1-4) CH₂
- G17 = alkyl <containing 1-10 C>
- G19 = alkylene <containing 1-4 C, unbranched>
(opt. substd. by 1 or more G15) / G16

G20 = H / alkyl <containing 1-10 C> /
 alkoxy <containing 1-10 C> / F / Cl / Br / I / CN /
 alkylthio <containing 1-10 C>
 G21 = H / Me / alkoxy <containing 1-10 C> / F / Cl / Br /
 I / CN
 G22 = alkylene <containing 2-6 C>
 (opt. substd. by 1 or more G10) / G23
 G23 = (2-6) CH2
 G24 = alkyl <containing 1-10 C>
 (opt. substd. by 1 or more G25) /
 cycloalkyl <containing 3-8 C>
 G25 = F / Cl / Br / I / OH / alkoxy <containing 1-10 C> /
 cycloalkyl <containing 3-8 C> / NH2 (opt. substd.)
 G26 = H / alkyl <containing 1-10 C> (substd. by OH) /
 alkyl <containing 1-10 C> (substd. by 1 or more F) / OH /
 alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> /
 alkylamino <containing 1-10 C> /
 dialkylamino <each alkyl containing 1-10 C> / F
 G27 = H / OH / alkyl <containing 1-10 C>
 (opt. substd. by OH) / F
 G28 = H / alkyl <containing 1-10 C> (opt. substd. by OH) /
 alkyl <containing 1-10 C> (substd. by 1 or more F)
 G29 = (1-5) 57

G30—C—G30
 57

G30 = H / OH / alkyl <containing 1-10 C> /
 alkoxy <containing 1-10 C> / alkylamino <containing 1-10 C> /
 dialkylamino <each alkyl containing 1-10 C> / F
 G35 = N / 252

C—G36
 252

G36 = H / alkyl <containing 1-10 C> /
 alkoxy <containing 1-10 C> / F / Cl / Br / I / OH / CN /
 alkylthio <containing 1-10 C>

G37 = H / Me

Patent location:

claim 1

Note:

substitution is restricted

Note:

or pharmaceutically acceptable salts, esters,
 amides, or prodrugs

L52 ANSWER 7 OF 14 MARPAT COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 143:477862 MARPAT

TITLE: Preparation of bicyclic amines bearing heterocyclic
 substituents as H3 receptor ligands

INVENTOR(S): Altenbach, Robert J.; Black, Lawrence A.; Chang,
 Sou-Jen; Cowart, Marlon D.; Faghih, Ramin; Gfesser,
 Gregory A.; Ku, Yi-Yin; Liu, Huaqing; Lukin, Kirill
 A.; Nersesian, Diana L.; Pu, Yu-Ming; Curtis, Michael
 P.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 41 pp.

CODEN: USXXCO

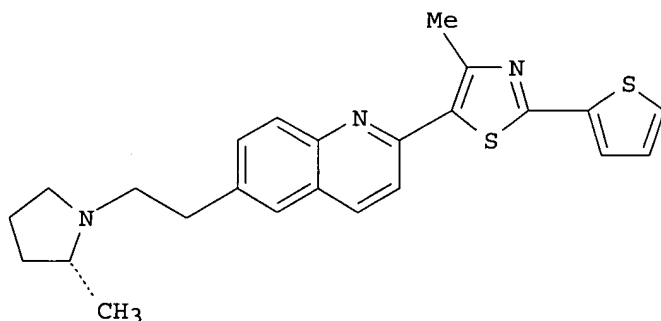
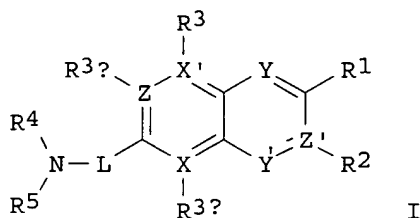
DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------|----------|-----------------|----------|
| US 2005256118 | A1 | 20051117 | US 2004-843742 | 20040512 |
| WO 2005113551 | A1 | 20051201 | WO 2005-US14863 | 20050429 |

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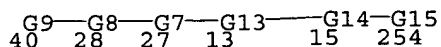
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PRIORITY APPLN. INFO.: US 2004-843742 20040512
 GI

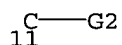


AB Title compds. I [Y, Y' = CH, CF, N; X, X', Z, Z' = C, N; R1, R2 = H, alkyl, alkoxy, aryl, cycloalkyl, etc.; R3 = absent when X' is N or H, alkyl, alkoxy, etc.; R3b = absent when Z is N or H, alkyl, alkoxy, halo, etc.; R4-5 = alkyl, haloalkyl, hydroxyalkyl, etc.; L = divalent alkyl, etc.] are prepared For instance, II is prepared in 7 steps from (S)-(5-oxopyrrolidin-2-yl)methyl 4-methylbenzenesulfonate, 1-(2-bromoethyl)-4-nitrobenzene, trimethylacetyl chloride, DMF and

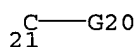
1-(4-methyl-2-(thiophene-2-yl)thiazol-5-yl)ethanone. Representative compds. of the invention demonstrated binding affinities for the H3 receptor from about 810 nM to about 0.02 nM. I are useful for the treatment of conditions or disorders prevented by or ameliorated by histamine-3 receptor ligands. Also disclosed are pharmaceutical compns. comprising the histamine-3 receptor ligands, methods for using such compds. and compns., and a process for preparing compds. within the scope of formula (I).

MSTR 1A

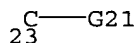
G1 = N / 11



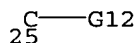
G2 = H / F
G3 = N / 21



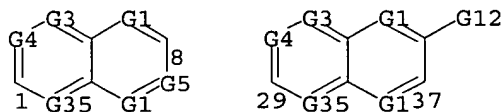
G4 = N / 23



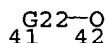
G5 = N / 25



G7 = 1-28 8-13 / 29-28 37-13

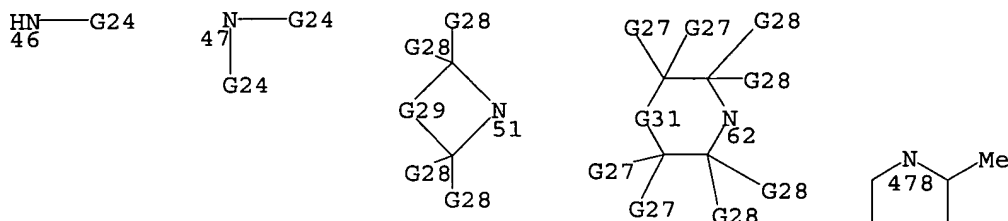


G8 = alkylene <containing 1-6 C>
(opt. substd. by 1 or more G10) / G11 / 41-40 42-27



G9 = NH2 / 46 / 47 / heterocycle <containing 5-13 atoms,
1-3 heteroatoms, 1 or more N, zero or more O,
zero or more S (no other heteroatoms),

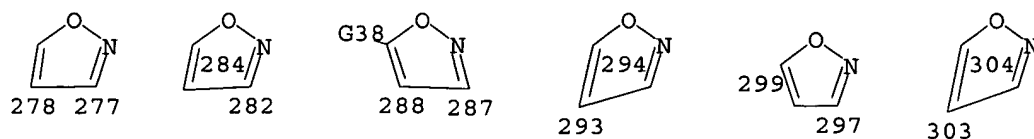
attached through 1 or more N, non-aromatic,
0 or more double bonds, mono- or bicyclic>
(opt. substd. by 1 or more G26) / 51 / 62 /
(Specifically claimed: 478)

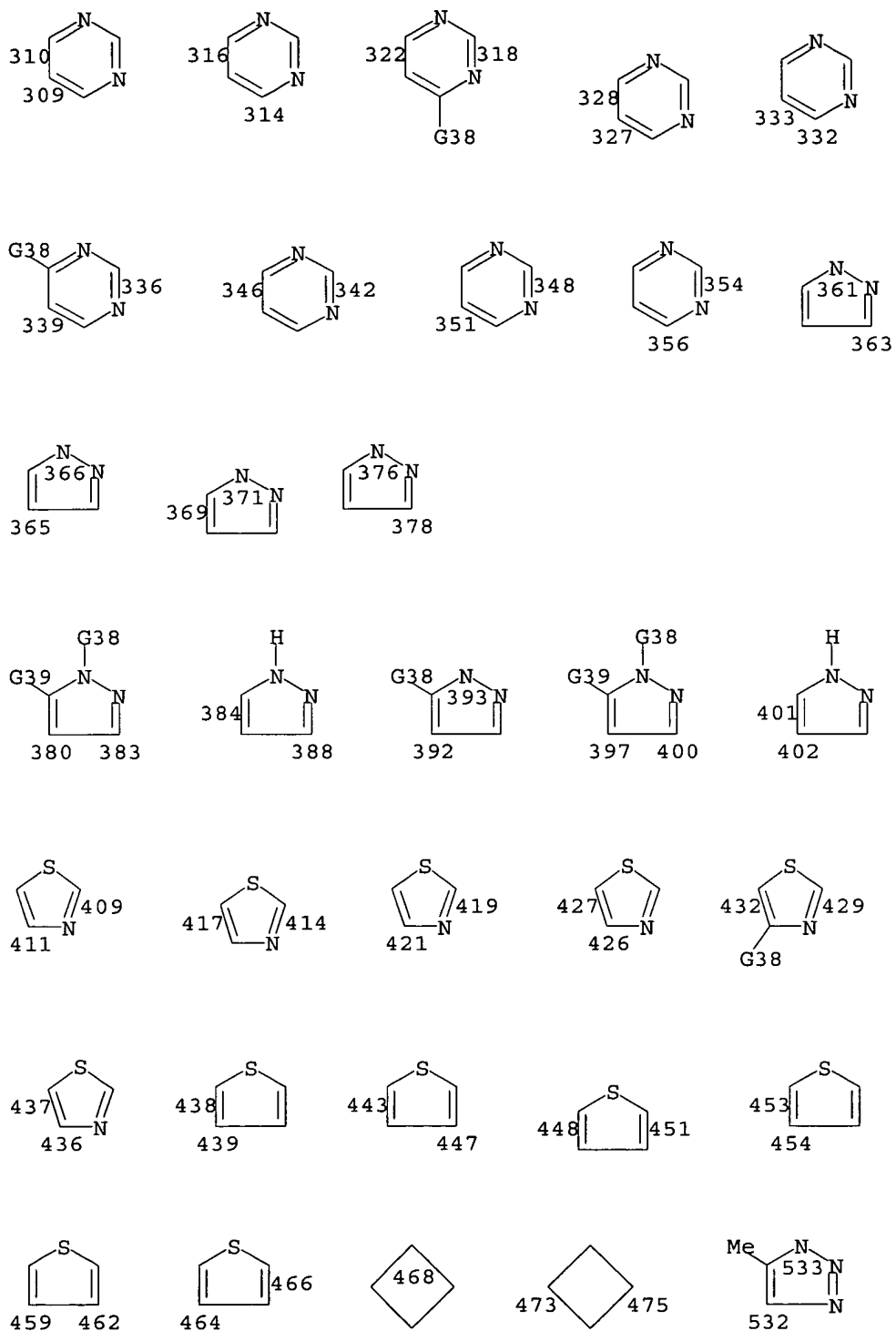


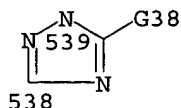
- G10 = alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F
G11 = (1-6) CH2
G12 = H / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / aryl (opt. substd.) /
cycloalkyl <containing 3-8 C> / F / Cl / Br / I / CN /
alkylthio <containing 1-10 C> / (Specifically claimed: Me)
G13 = O / C(O) / S / alkylene <containing 1-4 C,
unbranched> (opt. substd.) / NH / 16 / 18-27 19-15



- G14 = any ring <containing 5-8 atoms, zero or more N,
zero or more O, zero or more S> /
(Specifically claimed: phenylene / 277-13 278-254 /
282-13 284-254 / 288-13 287-254 / 293-13 294-254 /
299-13 297-254 / 304-13 303-254 / 310-13 309-254 /
316-13 314-254 / 322-13 318-254 / 327-13 328-254 /
333-13 332-254 / 339-13 336-254 / 342-13 346-254 /
348-13 351-254 / 354-13 356-254 / 361-13 363-254 /
366-13 365-254 / 371-13 369-254 / 378-13 376-254 /
383-13 380-254 / 388-13 384-254 / 392-13 393-254 /
397-13 400-254 / 402-13 401-254 / 409-13 411-254 /
414-13 417-254 / 421-13 419-254 / 426-13 427-254 /
432-13 429-254 / 437-13 436-254 / 438-13 439-254 /
443-13 447-254 / 448-13 451-254 / 454-13 453-254 /
459-13 462-254 / 464-13 466-254 / 468 / 473-13 475-254 /
heterocycle <containing 5 atoms, 3 N, 2 C, aromatic,
2 double bonds, 5-membered monocyclic ring> /
532-13 533-254 / 538-13 539-254)







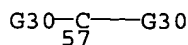
G15 = G37 / 255

~~G16-G37~~
255 256

G16 = R <"linking group"> / (Specifically claimed: 271-15
272-256 / 273-15 274-256)



- G17 = alkyl <containing 1-10 C>
 G19 = alkylene <containing 1-4 C, unbranched>
 (opt. substd.)
 G20 = H / alkyl <containing 1-10 C> /
 alkoxy <containing 1-10 C> / F / Cl / Br / I / CN /
 alkylthio <containing 1-10 C>
 G21 = H / Me / alkoxy <containing 1-10 C> / F / Cl / Br /
 I / CN
 G22 = alkylene <containing 2-6 C>
 (opt. substd. by 1 or more G10) / G23
 G23 = (2-6) CH2
 G24 = alkyl <containing 1-10 C>
 (opt. substd. by 1 or more G25) /
 cycloalkyl <containing 3-8 C>
 G25 = F / Cl / Br / I / OH / alkoxy <containing 1-10 C> /
 cycloalkyl <containing 3-8 C> / NH2 (opt. substd.)
 G26 = H / alkyl <containing 1-10 C> (substd. by OH) /
 alkyl <containing 1-10 C> (substd. by 1 or more F) / OH /
 alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> /
 alkylamino <containing 1-10 C> /
 dialkylamino <each alkyl containing 1-10 C> / F /
 alkyl <containing 1-10 C> / alkylcarbonyl <containing 1-10 C>
 / CONH2 / CHO / alkylaminocarbonyl <containing 1-10 C> /
 dialkylaminocarbonyl <each alkyl containing 1-10 C>
 G27 = H / OH / alkyl <containing 1-10 C>
 (opt. substd. by OH) / F
 G28 = H / alkyl <containing 1-10 C> (opt. substd. by OH) /
 alkyl <containing 1-10 C> (substd. by 1 or more F)
 G29 = (1-5) 57



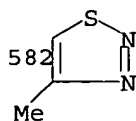
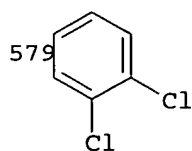
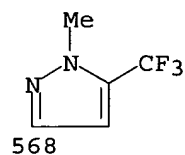
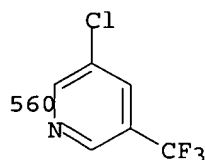
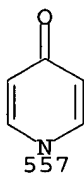
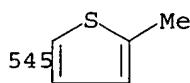
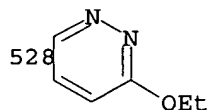
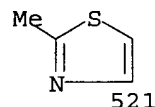
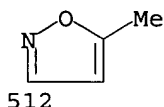
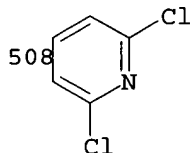
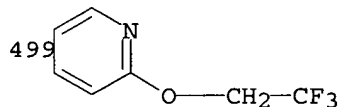
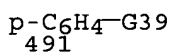
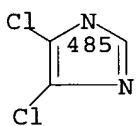
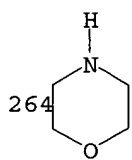
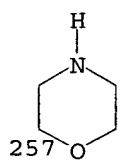
- G30 = H / OH / alkyl <containing 1-10 C> /
 alkoxy <containing 1-10 C> / alkylamino <containing 1-10 C> /
 dialkylamino <each alkyl containing 1-10 C> / F
 G31 = bond / O / S / 73

$\text{N} \text{---} \text{G32}$
73

G32 = H / alkyl <containing 1-10 C> /
alkylcarbonyl <containing 1-10 C> / CONH2 / CHO /
alkylaminocarbonyl <containing 1-10 C> /
dialkylaminocarbonyl <each alkyl containing 1-10 C>
G35 = N / 252

$\text{C} \text{---} \text{G36}$
252

G36 = H / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F / Cl / Br / I / OH / CN /
alkylthio <containing 1-10 C>
G37 = any ring <containing 5-8 atoms, zero or more N,
zero or more O, zero or more S> /
(Specifically claimed: isoxazolyl / morpholino / 257 / 264 /
491 / pyridazinyl / pyridyl / pyrimidinyl / pyrazinyl /
pyrazolyl / thiadiazolyl / thiazolyl / thienyl / triazolyl /
cyclobutyl / pyrrolidino / 485 / 499 / 508 / 512 / 521 /
528 / 545 / piperidino / 557 / 560 / 568 / 579 / 582)



G38 = H / Me
G39 = H / Cl

Patent location:

claim 1

Note:

substitution is restricted

Note:

or pharmaceutically acceptable salts, esters, amides, or prodrugs

L52 ANSWER 8 OF 14 MARPAT COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 141:71458 MARPAT

TITLE: Preparation of quinoline compounds for use in MCH receptor related disorders

INVENTOR(S): Frimurer, Thomas Michael; Ulven, Trond; Hoegberg, Thomas; Norregaard, Pja Karina; Little, Paul Brian; Receveur, Jean-Marie

PATENT ASSIGNEE(S): 7TM Pharma A/S, Den.

SOURCE: PCT Int. Appl., 217 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

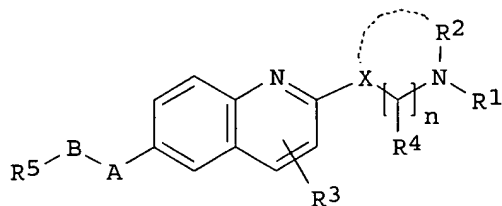
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

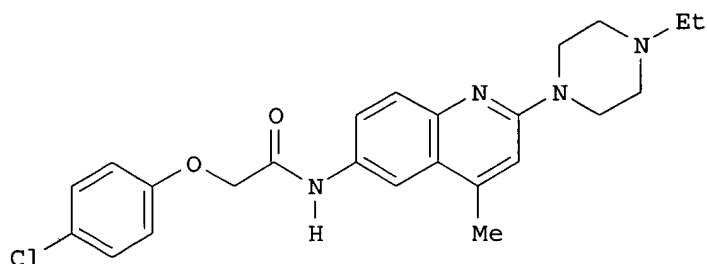
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--|----------|-----------------|----------|
| WO 2004052370 | A2 | 20040624 | WO 2003-DK857 | 20031211 |
| WO 2004052370 | A3 | 20040819 | | |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | |
| RW: | BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| CA 2508681 | AA | 20040624 | CA 2003-2508681 | 20031211 |
| AU 2003287878 | A1 | 20040630 | AU 2003-287878 | 20031211 |
| EP 1572212 | A2 | 20050914 | EP 2003-779716 | 20031211 |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | |
| US 2006111357 | A1 | 20060525 | US 2005-538455 | 20050902 |
| PRIORITY APPLN. INFO.: | | | DK 2002-1900 | 20021211 |
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GI



I

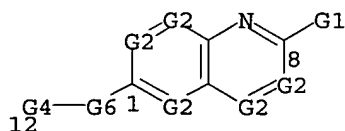


II

AB The present invention relates to the use of quinoline compds. I [A = CR7:CR7CONR7, YCR7CONR7, CONR7CONR7, etc. (wherein Y = CHR7, O, S, NR7; R7 = H, alkyl, alkenyl; R7 can be linked direct or via heteroatoms to B or the quinoline ring system when chemical feasible); X = N, C, O, S and X being restricted to N or C when linked to R2; B = (hetero)aryl; R1, R2 = H, alkyl, cycloalkyl, etc.; R4 = H, alkyl; R3 = H, alkyl, halo, etc.; R1, R2, R3 or R4 may optionally be linked to each other, or to the carbon chain linking the two N atoms, when possible, and O or NR1 may be inserted in the chain or ring; R4 may optionally be linked to X; R5 = H, halo, alkyl, etc.; n = 0-3; with provisos] for the preparation of a pharmaceutical and/or a cosmetic composition for the treatment, prophylaxis and/or diagnosis of a condition caused by or involving a melanin-concentrating hormone. The invention

also relates to novel quinoline compds. per se. The synthesis of the compds. I and their intermediates is described in 184 synthetic examples. E.g., a 4-step synthesis of II, starting from 2-chlorolepidine and N-ethylpiperazine, which showed IC50 of 20 nM against MCH-1 receptor binding, was given. The quinoline compds. I have been found to interact with a melanin-concentrating hormone receptor, a MCH receptor. The compds. I have modulating activity on the MCH receptor such as e.g. antagonistic, agonistic or allosteric activity and are useful for medicinal or cosmetic purposes such as, e.g. in the treatment or prevention of feeding disorders like obesity, metabolic syndrome, Type II diabetes, bulimia, etc. or in the treatment or prevention of depression.

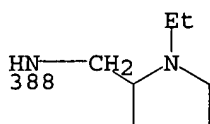
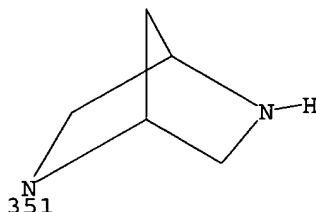
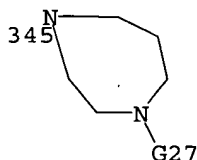
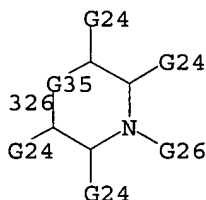
MSTR 1



G1 = heterocycle <containing 5 or more atoms,
2 or more N, attached through 2 or more N>

(opt. substd. by G25) / **318** / (Specifically claimed: 326) /
(Examples: 345 / 351 / 388)

G22-G23
318 319



G2 = N / 13

C-G3
13

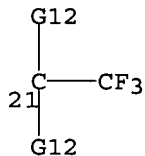
G3 = H / R / (Specifically claimed: Me) / (Example: Et)

G4 = aryl (opt. substd. by 1 or more G5) /
heteroaryl (opt. substd. by 1 or more G5) /
(Specifically claimed: Ph (opt. substd. by 1 or more G5) /
pyridyl (opt. substd. by 1 or more G5))

G5 = R / (Specifically claimed: halo /
alkyl <containing 1-6 C> / alkenyl <containing 2-6 C> /
alkynyl <containing 2-6 C> / cycloalkyl <containing 3-7 C> /
(opt. substd. by G10) / 16 / alkylamino <containing 1-10 C> /
dialkylamino <each alkyl containing 1-10 C> /
alkylaminocarbonyl <containing 1-10 C> /
dialkylaminocarbonyl <each alkyl containing 1-10 C> /
alkylcarbonylamino <containing 1-10 C> /
alkylcarbonyl <containing 1-10 C> / 19 / SMe /
alkyl <containing 1-10 C> (substd. by 1 or more F) / CF3 /
28 / 21) / (Example: Cl)

O-G11
16

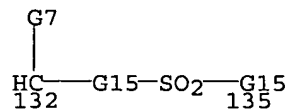
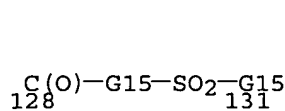
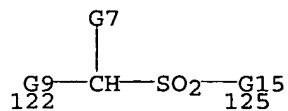
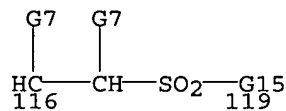
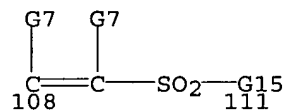
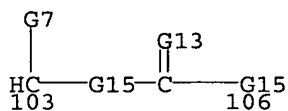
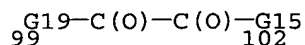
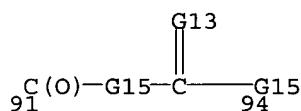
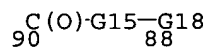
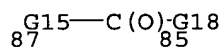
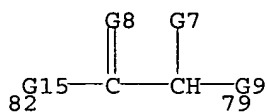
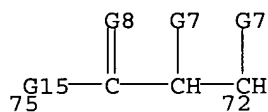
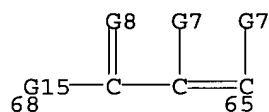
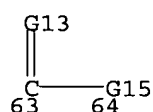
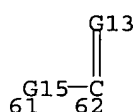
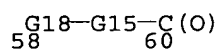
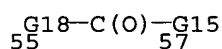
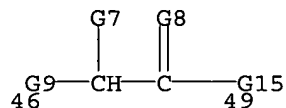
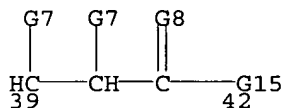
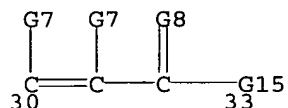
F₃C-N-CF₃
19

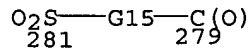
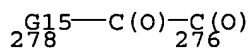
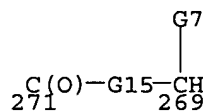
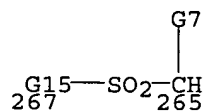
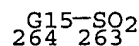
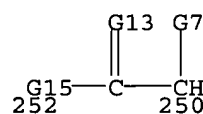
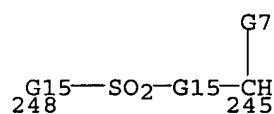
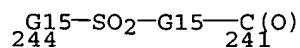
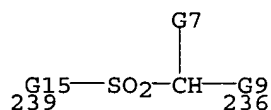
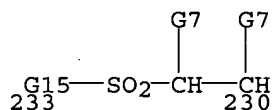
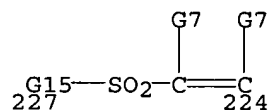
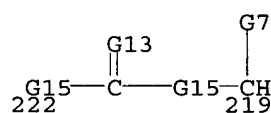
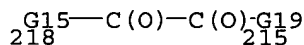
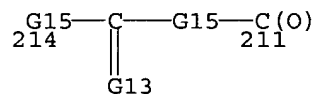
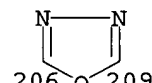
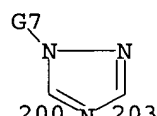
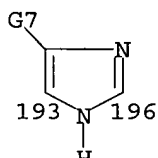
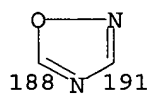
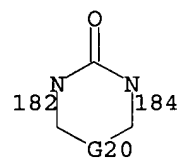
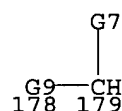
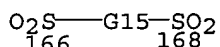
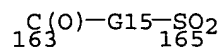
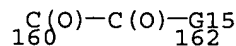
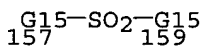
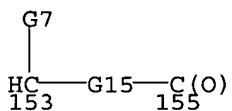
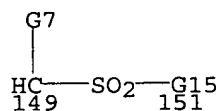
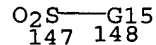
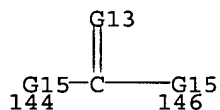
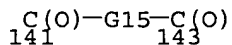
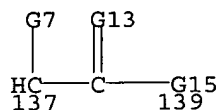


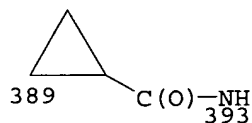
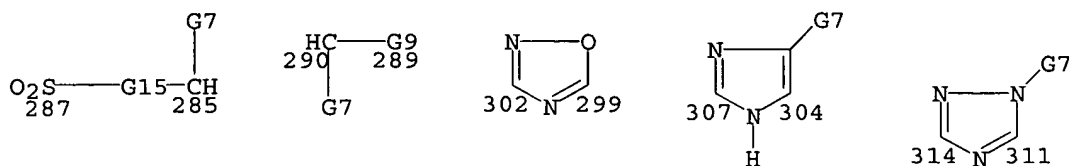
G13-G14
28

G6 = 30-12 33-1 / 39-12 42-1 / **46-12 49-1** /
55-12 57-1 / 58-12 60-1 / 63-12 64-1 / 61-12 62-1 /
68-12 65-1 / 75-12 72-1 / 82-12 79-1 / 87-12 85-1 /
90-12 88-1 / 91-12 94-1 / 99-12 102-1 / 103-12 106-1 /
108-12 111-1 / 116-12 119-1 / 122-12 125-1 /
128-12 131-1 / 132-12 135-1 / 137-12 139-1 /
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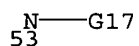
149-12 151-1 / 153-12 155-1 / 157-12 159-1 /
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 169-12 171-1 / CH=CH / 178-12 179-1 / 182-12 184-1 /
 188-12 191-1 / 193-12 196-1 / 200-12 203-1 /
 206-12 209-1 / 214-12 211-1 / 218-12 215-1 /
 222-12 219-1 / 227-12 224-1 / 233-12 230-1 /
 239-12 236-1 / 244-12 241-1 / 248-12 245-1 /
 252-12 250-1 / 264-12 263-1 / 267-12 265-1 /
 271-12 269-1 / 278-12 276-1 / 281-12 279-1 /
 287-12 285-1 / 290-12 289-1 / 302-12 299-1 /
 307-12 304-1 / 314-12 311-1 / (Example: 389-12 393-1)



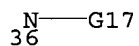




G7 = H / alkyl <containing 1-4 C> /
alkenyl <containing 2-4 C>
G8 = O / S
G9 = O / S / NH / 53



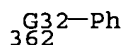
G10 = alkyl <containing 1-10 C>
G11 = alkyl <containing 1-10 C>
G12 = H / F
G13 = O / S
G14 = CF₃ / alkyl <containing 1-10 C>
(substd. by 1 or more F)
G15 = NH / 36



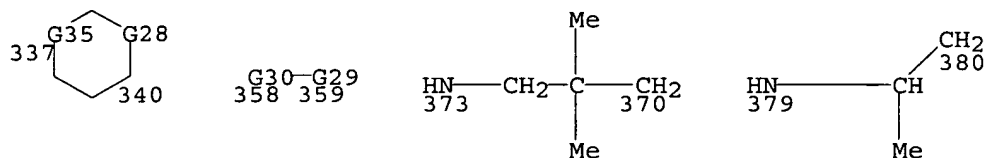
G17 = alkyl <containing 1-4 C> /
alkenyl <containing 2-4 C>
G18 = arylene / heteroarylene
G19 = 95 / O / S / NH / 97



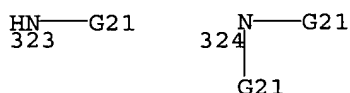
G20 = bond / CH₂
G21 = alkenyl <containing 2-6 C> /
alkynyl <containing 2-6 C> / alkyl <containing 1-6 C>
(opt. substd. by OH) / cycloalkyl <containing 3-6 C>
(opt. substd. by OH) / cycloalkyl <containing 3-7 C>
(opt. substd. by G10) / alkyl <containing 1-10 C>
(substd. by 1 or more G33) / 362 /
(Specifically claimed: Me / Et / Pr-n / Bu-n / Pr-i / Bu-i /
cyclopentyl / Bu-t / Bu-s / CH₂CH₂OH)



G22 = heterocycle <containing 5 or more atoms,
1 or more N, attached through 1 or more N>
(opt. substd. by G24) / 358-8 359-319 /
(Specifically claimed: 337-8 340-319) /
(Examples: 373-8 370-319 / 379-8 380-319)



G23 = NH2 / 323 / 324 / (Examples: pyrrolidino /
morpholino / piperidino)



G24 = alkyl <containing 1-4 C>
(opt. substd. by (1-2) alkyl <containing 1-4 C>) /
(Example: Me)

G25 = alkenyl <containing 2-6 C> /
alkynyl <containing 2-6 C> / alkyl <containing 1-6 C>
(opt. substd. by OH) / cycloalkyl <containing 3-6 C>
(opt. substd. by OH) / cycloalkyl <containing 3-7 C>
(opt. substd. by G10) / alkyl <containing 1-10 C>
(substd. by 1 or more G33) / 366

G32-Ph
366

G26 = alkenyl <containing 2-6 C> /
alkynyl <containing 2-6 C> / alkyl <containing 1-6 C>
(opt. substd. by OH) / cycloalkyl <containing 3-6 C>
(opt. substd. by OH) / cycloalkyl <containing 3-7 C>
(opt. substd. by G10) / alkyl <containing 1-10 C>
(substd. by 1 or more G33) / 364 /
(Specifically claimed: alkyl <containing 1-6 C>
(opt. substd. by OH) / cycloalkyl <containing 3-6 C>
(opt. substd. by OH) / Me / Et / Pr-n / Bu-n / Pr-i / Bu-i /
cyclopentyl / Bu-t / Bu-s / CH2CH2OH)

G32-Ph
364

G27 = H / Me
G28 = CH2 / (Example: bond)
G29 = G34 / alkylene <containing 1-3 C>
(opt. substd. by alkyl <containing 1 or more C>)
G30 = NH / 360 / O / S / CH2 (opt. substd.)

N-G31
360

G31 = R / (Example: Me)
G32 = (1-3) CH2
G33 = aryl / heteroaryl
G34 = (0-3) CH2
G35 = CH / N

Patent location: claim 1
Note: substitution is restricted
Note: additional derivatization also claimed

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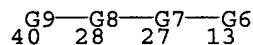
ACCESSION NUMBER: 141:7138 MARPAT
TITLE: Preparation of bicyclic-substituted amines as
histamine-3 receptor ligands
INVENTOR(S): Altenbach, Robert J.; Black, Lawrence A.; Chang,
Sou-Jen; Cowart, Marlon D.; Faghih, Ramin; Gfesser,
Gregory A.; Ku, Yi-Yin; Liu, Huaqing; Lukin, Kirill
A.; Nersesian, Diana L.; Pu, Yu-Ming; Sharma, Padam
N.; Bennani, Youssef L.; Curtis, Michael P.
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: PCT Int. Appl., 229 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--|----------|------------------|----------|
| WO 2004043458 | A1 | 20040527 | WO 2003-US335365 | 20031105 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW | | | |
| RW: | BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| US 2004092521 | A1 | 20040513 | US 2002-292422 | 20021112 |
| US 2004152704 | A1 | 20040805 | US 2003-689735 | 20031022 |
| CA 2505427 | AA | 20040527 | CA 2003-2505427 | 20031105 |
| AU 2003291329 | A1 | 20040603 | AU 2003-291329 | 20031105 |
| EP 1569637 | A1 | 20050907 | EP 2003-768721 | 20031105 |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | |
| JP 2006514926 | T2 | 20060518 | JP 2004-551799 | 20031105 |
| PRIORITY APPLN. INFO.: | | | US 2002-292422 | 20021112 |
| | | | US 2002-425376P | 20021112 |
| | | | US 2003-689735 | 20031022 |
| | | | WO 2003-US35365 | 20031105 |

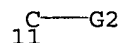
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

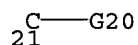
AB Title compds. I [wherein Y, and B = independently CH, CF, or N; X, A, Z, and C = independently C or N; one of R1 and R2 = halo, CN, aryl, aryloxy, etc.; the other of R1 and R2 = H, cyclo/alkyl, thio/alkoxy, aryl, halo, CN, provided that R2 is absent when C = N; R3 = H, alkyl, alkoxy, absent, etc.; R = absent, H, halo, Me, alkoxy, or CN; R6 = absent, H, alkyl, thio/alkoxy, halo, OH, CN; R4 and R5 = independently alkyl, haloalkyl, hydroxyalkyl, or NR4R5 = (un)1-pyrrolidinyl, 1-piperidinyl, 1-morpholinyl, etc.; L = (un)substituted alkylene or -alkylene-O-; their pharmaceutically acceptable salts, esters, amides, or prodrugs] were prepared as histamine-3 receptor ligands. For example, quinoxaline II was prepared in 6 steps via cyclocondensation of benzenediamine III with glyoxal in EtOH, followed by reaction with oxo(phenyl)acetaldehyde. Selected I showed binding affinities of 0.12 to 20 nM towards histamine-3 receptors in rats. I are useful for the treatment of memory disorder, cognition disorder, obesity, etc. (no data).

MSTR 1A

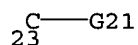
G1 = N / 11



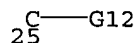
G2 = H / F
G3 = N / 21



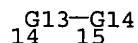
G4 = N / 23



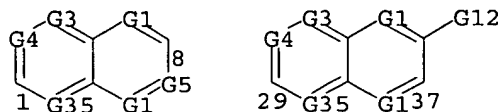
G5 = N / 25



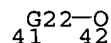
G6 = 14 / F / Cl / Br / I / CN



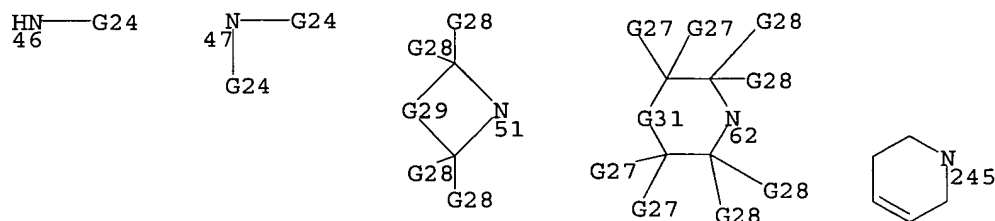
G7 = 1-28 8-13 / 29-28 37-13



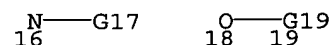
G8 = alkylene <containing 1-6 C>
(opt. substd. by 1 or more G10) / G11 / 41-40 42-27



G9 = NH2 / 46 / 47 / heterocycle <containing 5-13 atoms,
1-3 heteroatoms, 1 or more N, zero or more O,
zero or more S (no other heteroatoms),
attached through 1 or more N, non-aromatic,
0 or more double bonds, mono- or bicyclic>
(opt. substd. by 1 or more G26) / 51 / 62 /
(Specifically claimed: pyrrolidino (opt. substd. by G41) /
245)



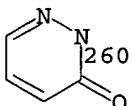
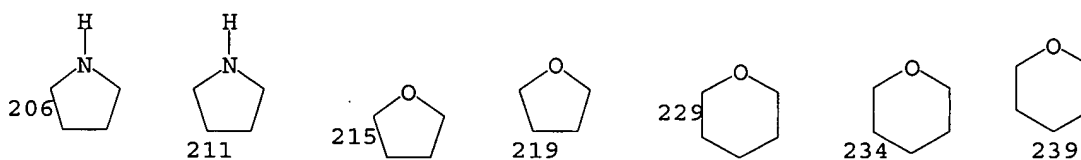
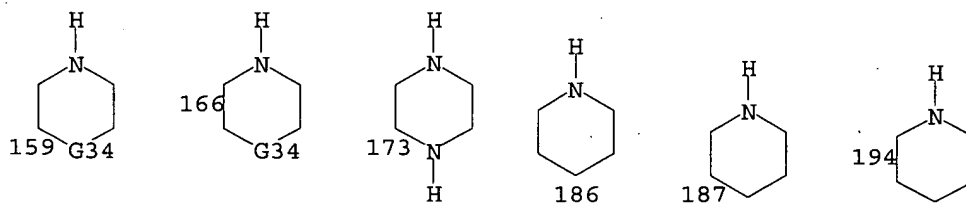
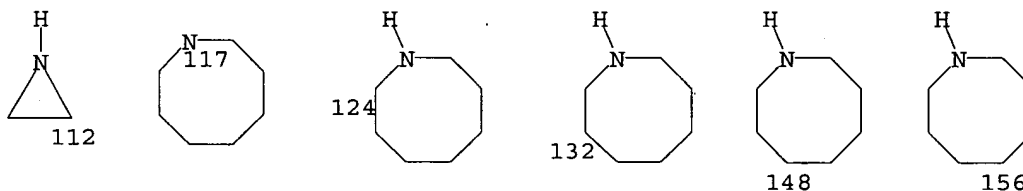
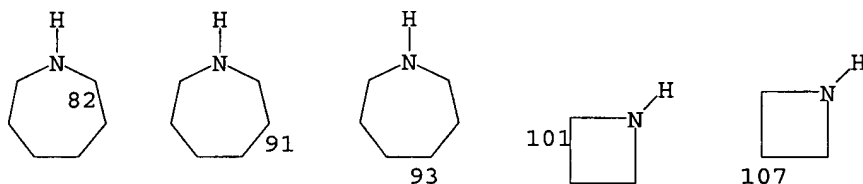
G10 = alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F
G11 = (1-6) CH2
G12 = H / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / Ph (opt. substd.) /
cycloalkyl <containing 3-8 C> / F / Cl / Br / I / CN /
alkylthio <containing 1-10 C>
G13 = O / C(O) / S / alkylene <containing 1-4 C,
unbranched> (opt. substd. by 1 or more G15) / G16 / NH / 16
/ 18-27 19-15 / (Specifically claimed: CHOH)



G14 = Ph (opt. substd. by G37) /
heteroaryl <containing 1-4 heteroatoms, zero or more N,
zero or more O, zero or more S (no other heteroatoms),
monocyclic> / heterocycle <containing 3-8 atoms,
1-3 heteroatoms, zero or more N, zero or more O,
zero or more S (no other heteroatoms), monocyclic>
(opt. substd. by 1 or more G39) /
cycloalkyl <containing 3-8 C> /
(Specifically claimed: furyl / imidazolyl / isoxazolyl /
isothiazolyl / oxadiazolyl / oxazolyl / pyrazinyl /
pyrazolyl / pyridazinyl / 75 / pyridyl / pyrimidinyl /

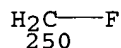
pyrrolyl / tetrazolyl / thiadiazolyl / thiazolyl / thienyl /
 triazinyl / triazolyl / hexahydroazepino / 82 / 91 / 93 /
 azetidino / 101 / 107 / aziridino / 112 / 117 / 124 / 132 /
 148 / 156 / morpholino / 159 / 166 / piperazino / 173 /
 piperidino / 186 / 187 / 194 / pyrrolidino / 206 / 211 /
 heterocycle <containing 1 heteroatom, 1 N, 4 C,
 non-aromatic, 1 double-exact bond,
 5-membered monocyclic ring> / thiomorpholino / 215 / 219 /
 229 / 234 / 239 / 260)

G33=O
 75

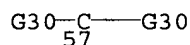


G15 = OH / alkyl <containing 1-10 C> /
 alkoxy <containing 1-10 C> / F
 G16 = (1-4) CH₂

- G17 = alkyl <containing 1-10 C>
 G19 = alkylene <containing 1-4 C, unbranched>
 (opt. substd. by 1 or more G15) / G16
 G20 = H / alkyl <containing 1-10 C> /
 alkoxy <containing 1-10 C> / F / Cl / Br / I / CN /
 alkylthio <containing 1-10 C>
 G21 = H / Me / alkoxy <containing 1-10 C> / F / Cl / Br /
 I / CN
 G22 = alkylene <containing 2-6 C>
 (opt. substd. by 1 or more G10) / G23
 G23 = (2-6) CH₂
 G24 = alkyl <containing 1-10 C>
 (opt. substd. by 1 or more G25) /
 cycloalkyl <containing 3-8 C> / (Specifically claimed: Me /
 Et / Pr-n)
 G25 = F / Cl / Br / I / OH / alkoxy <containing 1-10 C> /
 cycloalkyl <containing 3-8 C> / NH₂ (opt. substd.)
 G26 = H / alkyl <containing 1-10 C> (substd. by OH) /
 alkyl <containing 1-10 C> (substd. by 1 or more F) / OH /
 alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> /
 alkylamino <containing 1-10 C> /
 dialkylamino <each alkyl containing 1-10 C> / F
 G27 = H / OH / alkyl <containing 1-10 C>
 (opt. substd. by OH) / F
 G28 = H / alkyl <containing 1-10 C> (opt. substd. by OH) /
 alkyl <containing 1-10 C> (substd. by 1 or more F) /
 (Specifically claimed: Me / Et / CH₂OH / 250)



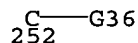
- G29 = (1-5) 57



- G30 = H / OH / alkyl <containing 1-10 C> /
 alkoxy <containing 1-10 C> / alkylamino <containing 1-10 C> /
 dialkylamino <each alkyl containing 1-10 C> / F
 G31 = bond / O / S / 73



- G32 = H / alkyl <containing 1-10 C> /
 alkylcarbonyl <containing 1-10 C> / CONH₂ / CHO /
 alkylaminocarbonyl <containing 1-10 C> /
 dialkylaminocarbonyl <each alkyl containing 1-10 C>
 G33 = heterocycle <containing 2 heteroatoms, 2 N, 4 C,
 6-membered monocyclic ring>
 G34 = O / S
 G35 = N / 252



G36 = H / alkyl <containing 1-10 C> /
 alkoxy <containing 1-10 C> / F / Cl / Br / I / OH / CN /
 alkylthio <containing 1-10 C>
 G37 = R / CN / F / Cl / Br / I / NH₂ (opt. substd.) /
 alkoxy <containing 1-10 C> / alkyl <containing 1-10 C>
 (opt. substd. by OH) / alkylcarbonyl <containing 1-10 C> /
 alkoxy carbonyl <containing 1-10 C> /
 cycloalkylcarbonyl <containing 3-8 C> /
 alkylsulfonyl <containing 1-10 C> /
 alkylthio <containing 1-10 C> /
 alkyl <containing 1-10 C> (substd. by 1 or more G38)
 G38 = F / Cl / Br / I
 G39 = NH₂ (opt. substd.) / F / Cl / Br / I /
 alkyl <containing 1-10 C> (opt. substd. by 1 or more G38) /
 CN / 254 / alkoxy carbonyl <containing 1-10 C> /
 CONH₂ (opt. substd.) / alkylcarbonyl <containing 1-10 C> /
 alkoxy <containing 1-10 C>

HN—O—G40
 254

G40 = alkyl <containing 1-10 C>
 G41 = Me / Et / Pr-i / Bu-i / CH₂OH / NHMe / NMe₂ / 248

H₂C—F
 248

Patent location: claim 1
 Note: substitution is restricted
 Note: or pharmaceutically acceptable salts, esters,
 amides, or prodrugs

L52 ANSWER 10 OF 14 MARPAT COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 140:105259 MARPAT
 TITLE: Methods using a niclosamide compound and other agents
 for the treatment of neoplasms
 INVENTOR(S): Lee, Margaret S.; Keith, Curtis; Auspitz, Benjamin A.;
 Zimmermann, Grant R.; Nichols, M. James; Foley,
 Michael A.
 PATENT ASSIGNEE(S): Combinatorx, Incorporated, USA
 SOURCE: PCT Int. Appl., 75 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------|----------|-----------------|----------|
| WO 2004006906 | A2 | 20040122 | WO 2003-US22026 | 20030715 |
| WO 2004006906 | A3 | 20040304 | | |

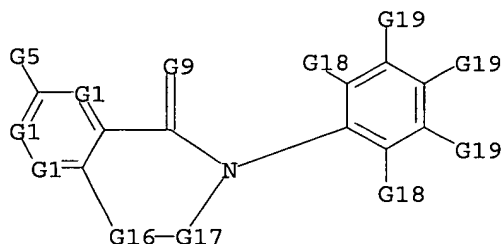
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 GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
 LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
 PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,

TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
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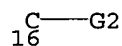
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 US 2002-396136P 20020715
 US 2002-400913P 20020802
 US 2002-400963P 20020802
 US 2003-460203P 20030403
 US 2003-460348P 20030403
 WO 2003-US22026 20030715

AB The invention features a method for treating a patient having a cancer or other neoplasm by administering a niclosamide, or a structural or functional analog thereof, and, optionally, one or more antiproliferative agents in an amount effective to inhibit the growth of the neoplasm.

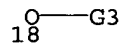
MSTR 1B



G1 = N / 16



G2 = H / OH / 18 / carbon chain <containing 1 or more C,
 0 or more double bonds, 0 or more triple bonds>
 (opt. substd.) / carbocycle <containing 3-7 C,
 0 or more double bonds, 0 or more triple bonds>
 (opt. substd.) / R <"heteroalkyl",
 containing zero or more N, zero or more O, zero or more S,
 zero or more P, 1-7 C> / F / Cl / Br / I / NO2

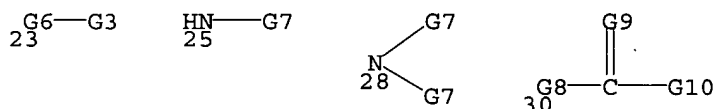


G3 = 20 / carbon chain <containing 1 or more C,
 0 or more double bonds, 0 or more triple bonds>
 (opt. substd.) / carbocycle <containing 3-7 C,
 0 or more double bonds, 0 or more triple bonds>
 (opt. substd.) / heterocycle <containing 5-14 atoms,
 1-4 heteroatoms, zero or more N, zero or more O,
 zero or more S (no other heteroatoms), mono- or bicyclic>
 (opt. substd.) / aryl <containing 6-12 C> (opt. substd.) /
 alkyl <containing 1-8 C> (substd. by 1 or more aryl

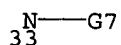
<containing 6-13 C> (opt. substd.)) /
 alkyl <containing 1-9 C> (substd. by heterocycle <containing
 zero or more N, zero or more O, zero or more S, up to 9 C>
 (opt. substd.)) / R <"heteroalkyl",
 containing zero or more N, zero or more O, zero or more S,
 zero or more P, 1-7 C>

^{C(O)}G4
 20

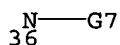
- G4 = carbon chain <containing 1 or more C,
 0 or more double bonds, 0 or more triple bonds>
 (opt. substd.) / carbocycle <containing 3-7 C,
 0 or more double bonds, 0 or more triple bonds>
 (opt. substd.) / heterocycle <containing 5-14 atoms,
 1-4 heteroatoms, zero or more N, zero or more O,
 zero or more S (no other heteroatoms), mono- or bicyclic>
 (opt. substd.) / aryl <containing 6-12 C> (opt. substd.) /
 alkyl <containing 1-8 C> (substd. by 1 or more aryl
 <containing 6-13 C> (opt. substd.)) /
 alkyl <containing 1-9 C> (substd. by heterocycle <containing
 zero or more N, zero or more O, zero or more S, up to 9 C>
 (opt. substd.)) / R <"heteroalkyl",
 containing zero or more N, zero or more O, zero or more S,
 zero or more P, 1-7 C>
- G5 = H / F / Cl / Br / I / OH / SH / 23 / NH2 / 25 / 28 /
 30



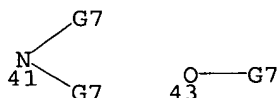
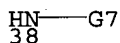
- G6 = O / S
- G7 = carbon chain <containing 1 or more C,
 0 or more double bonds, 0 or more triple bonds>
 (opt. substd.) / carbocycle <containing 3-7 C,
 0 or more double bonds, 0 or more triple bonds>
 (opt. substd.) / heterocycle <containing 5-14 atoms,
 1-4 heteroatoms, zero or more N, zero or more O,
 zero or more S (no other heteroatoms), mono- or bicyclic>
 (opt. substd.) / aryl <containing 6-12 C> (opt. substd.) /
 alkyl <containing 1-8 C> (substd. by 1 or more aryl
 <containing 6-13 C> (opt. substd.)) /
 alkyl <containing 1-9 C> (substd. by heterocycle <containing
 zero or more N, zero or more O, zero or more S, up to 9 C>
 (opt. substd.)) / R <"heteroalkyl",
 containing zero or more N, zero or more O, zero or more S,
 zero or more P, 1-7 C>
- G8 = NH / 33



- G9 = O / S / 36

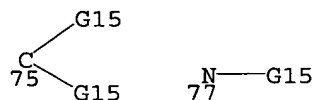


G10 = carbon chain <containing 1 or more C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / carbocycle <containing 3-7 C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / heterocycle <containing 5-14 atoms,
1-4 heteroatoms, zero or more N, zero or more O,
zero or more S (no other heteroatoms), mono- or bicyclic>
(opt. substd.) / aryl <containing 6-12 C> (opt. substd.) /
alkyl <containing 1-8 C> (substd. by 1 or more aryl
<containing 6-13 C> (opt. substd.)) /
alkyl <containing 1-9 C> (substd. by heterocycle <containing
zero or more N, zero or more O, zero or more S, up to 9 C>
(opt. substd.)) / R <"heteroalkyl",
containing zero or more N, zero or more O, zero or more S,
zero or more P, 1-7 C> / NH2 / 38 / 41 / 43

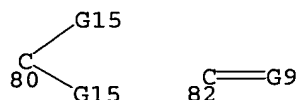


G15 = H / carbon chain <containing 1 or more C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / carbocycle <containing 3-7 C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / heterocycle <containing 5-14 atoms,
1-4 heteroatoms, zero or more N, zero or more O,
zero or more S (no other heteroatoms), mono- or bicyclic>
(opt. substd.) / aryl <containing 6-12 C> (opt. substd.) /
alkyl <containing 1-8 C> (substd. by 1 or more aryl
<containing 6-13 C> (opt. substd.)) /
alkyl <containing 1-9 C> (substd. by heterocycle <containing
zero or more N, zero or more O, zero or more S, up to 9 C>
(opt. substd.)) / R <"heteroalkyl",
containing zero or more N, zero or more O, zero or more S,
zero or more P, 1-7 C>

G16 = 75 / O / S / 77

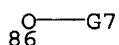


G17 = 80 / 82

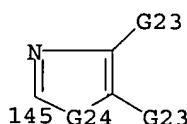
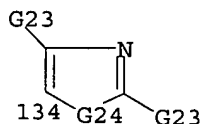
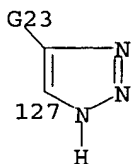
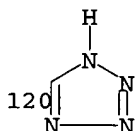
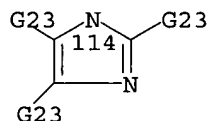
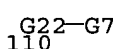
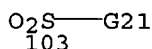
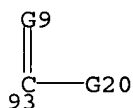
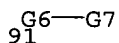


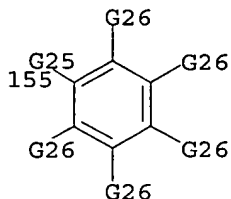
G18 = H / F / Cl / Br / I / CF3 / OH / 86 /
carbon chain <containing 1 or more C,

0 or more double bonds, 0 or more triple bonds>
 (opt. substd.) / carbocycle <containing 3-7 C,
 0 or more double bonds, 0 or more triple bonds>
 (opt. substd.) / heterocycle <containing 5-14 atoms,
 1-4 heteroatoms, zero or more N, zero or more O,
 zero or more S (no other heteroatoms), mono- or bicyclic>
 (opt. substd.) / aryl <containing 6-12 C> (opt. substd.) /
 alkyl <containing 1-8 C> (substd. by 1 or more aryl
 <containing 6-13 C> (opt. substd.)) /
 alkyl <containing 1-9 C> (substd. by heterocycle <containing
 zero or more N, zero or more O, zero or more S, up to 9 C>
 (opt. substd.)) / R <"heteroalkyl",
 containing zero or more N, zero or more O, zero or more S,
 zero or more P, 1-7 C>

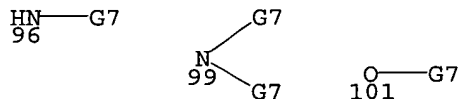


G19 = H / carbon chain <containing 1 or more C,
 0 or more double bonds, 0 or more triple bonds>
 (opt. substd.) / carbocycle <containing 3-7 C,
 0 or more double bonds, 0 or more triple bonds>
 (opt. substd.) / heterocycle <containing 5-14 atoms,
 1-4 heteroatoms, zero or more N, zero or more O,
 zero or more S (no other heteroatoms), mono- or bicyclic>
 (opt. substd.) / aryl <containing 6-12 C> (opt. substd.) /
 alkyl <containing 1-8 C> (substd. by 1 or more aryl
 <containing 6-13 C> (opt. substd.)) /
 alkyl <containing 1-9 C> (substd. by heterocycle <containing
 zero or more N, zero or more O, zero or more S, up to 9 C>
 (opt. substd.)) / R <"heteroalkyl",
 containing zero or more N, zero or more O, zero or more S,
 zero or more P, 1-7 C> / F / Cl / Br / I / NO₂ / CO₂H /
 SO₃H / CF₃ / CN / OH / SH / 91 / 93 / 103 / 110 / 114 / 120 /
 127 / 134 / 145 / 155

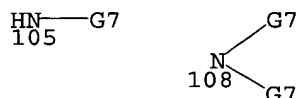




G20 = NH2 / 96 / 99 / 101



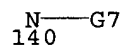
G21 = NH2 / 105 / 108



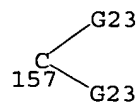
G22 = S(O) / SO2

G23 = H / F / Cl / Br / I / CN / NO2 / CF3 /
carbon chain <containing 1 or more C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / carbocycle <containing 3-7 C,
0 or more double bonds, 0 or more triple bonds>
(opt. substd.) / heterocycle <containing 5-14 atoms,
1-4 heteroatoms, zero or more N, zero or more O,
zero or more S (no other heteroatoms), mono- or bicyclic>
(opt. substd.) / aryl <containing 6-12 C> (opt. substd.) /
alkyl <containing 1-8 C> (substd. by 1 or more aryl
<containing 6-13 C> (opt. substd.)) /
alkyl <containing 1-9 C> (substd. by heterocycle <containing
zero or more N, zero or more O, zero or more S, up to 9 C>
(opt. substd.)) / R <"heteroalkyl",
containing zero or more N, zero or more O, zero or more S,
zero or more P, 1-7 C>

G24 = O / S / 140



G25 = O / S / 157



G26 = 2 or more H / F / Cl / Br / I / CN / NO2 / CF3 /
carbon chain <containing 1 or more C,
0 or more double bonds, 0 or more triple bonds>

(opt. substd.) / carbocycle <containing 3-7 C,
 0 or more double bonds, 0 or more triple bonds>
 (opt. substd.) / heterocycle <containing 5-14 atoms,
 1-4 heteroatoms, zero or more N, zero or more O,
 zero or more S (no other heteroatoms), mono- or bicyclic>
 (opt. substd.) / aryl <containing 6-12 C> (opt. substd.) /
 alkyl <containing 1-8 C> (substd. by 1 or more aryl
 <containing 6-13 C> (opt. substd.)) /
 alkyl <containing 1-9 C> (substd. by heterocycle <containing
 zero or more N, zero or more O, zero or more S, up to 9 C>
 (opt. substd.)) / R <"heteroalkyl",
 containing zero or more N, zero or more O, zero or more S,
 zero or more P, 1-7 C>

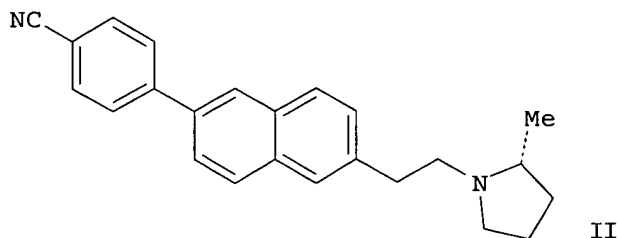
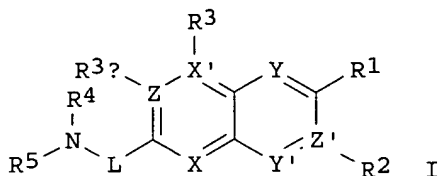
Patent location: claim 1
 Note: or salts

L52 ANSWER 11 OF 14 MARPAT COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 140:406732 MARPAT
 TITLE: Preparation of pyrrolidine derivatives as histamine-3
 receptor ligands
 INVENTOR(S): Altenbach, Robert J.; Black, Lawrence A.; Chang,
 Sou-jen; Cowart, Marlon D.; Faghih, Ramin; Gfesser,
 Gregory A.; Ku, Yi-yin; Liu, Huaqing; Lukin, Kirill
 A.; Nersesian, Diana L.; Pu, Yu-ming; Sharma, Padam
 N.; Bennani, Youssef L.
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 55 pp.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

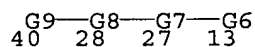
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|----------|
| US 2004092521 | A1 | 20040513 | US 2002-292422 | 20021112 |
| CA 2505427 | AA | 20040527 | CA 2003-2505427 | 20031105 |
| WO 2004043458 | A1 | 20040527 | WO 2003-US35365 | 20031105 |
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| RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2003291329 | A1 | 20040603 | AU 2003-291329 | 20031105 |
| EP 1569637 | A1 | 20050907 | EP 2003-768721 | 20031105 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| JP 2006514926 | T2 | 20060518 | JP 2004-551799 | 20031105 |
| PRIORITY APPLN. INFO.: | | | | |
| | | | US 2002-292422 | 20021112 |
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GI

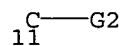


AB The title compds. I [wherein X, Y, and Y' = independently CH, CF, or N; X', Z, and Z' = independently C or N; R1 and R2 = independently halo, CN, H, alkyl, alkoxy, etc.; R3 = H, alkyl, alkoxy, absent, etc.; R3a = absent, H, halo, Me, alkoxy, or CN; R4 and R5 = independently alkyl, haloalkyl, hydroxyalkyl, etc.; L = (un)substituted alkylene or -alkylene-O-] or pharmaceutically acceptable salts, esters, amides, or prodrugs thereof are prepared as histamine-3 receptor ligands. For example, the compound II was prepared in a multi-step synthesis. Some of compds. I showed binding affinities of 0.12 to 20 nM towards histamine-3 receptors in rat. I are useful for the treatment of memory disorder, cognition disorder, obesity, etc. (no data).

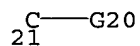
MSTR 1A



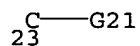
G1 = N / 11



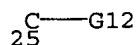
G2 = H / F
G3 = N / 21



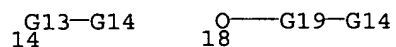
G4 = N / 23



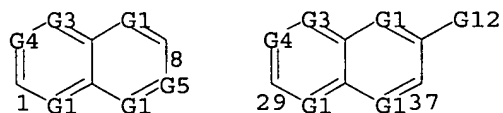
G5 = N / 25



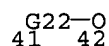
G6 = 14 / 18 / F / Cl / Br / I / CN



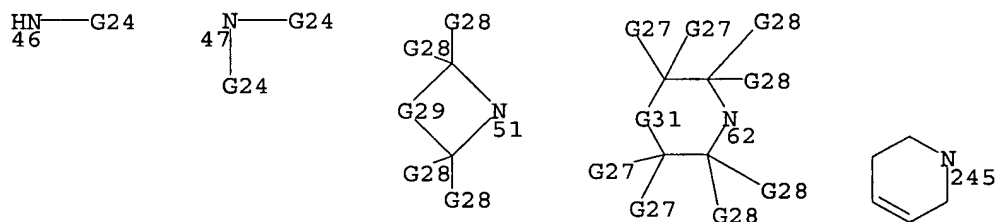
G7 = 1-28 8-13 / 29-28 37-13



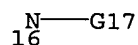
G8 = alkylene <containing 1-6 C>
(opt. substd. by 1 or more G10) / G11 / 41-40 42-27



G9 = NH2 / 46 / 47 / heterocycle <containing 5-13 atoms,
1-3 heteroatoms, 1 or more N, zero or more O,
zero or more S (no other heteroatoms),
attached through 1 or more N, non-aromatic,
0 or more double bonds, mono- or bicyclic>
(opt. substd. by 1 or more G26) / 51 / 62 /
(Specifically claimed: 245 / pyrrolidino (opt. substd. by
G35))

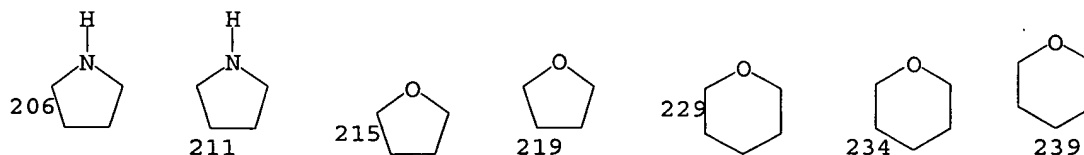
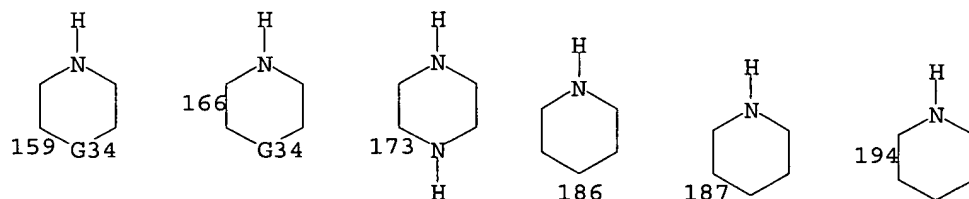
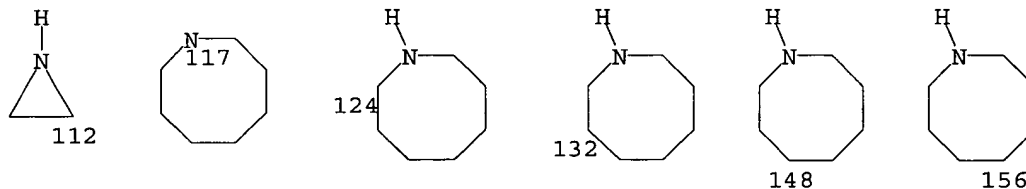
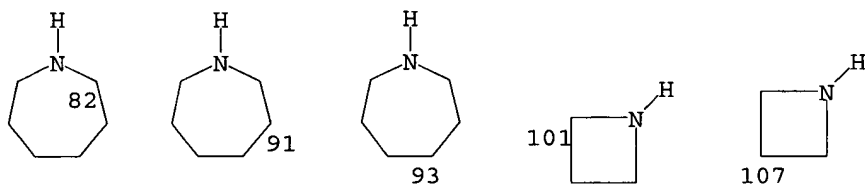


G10 = alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F
G11 = (1-6) CH2
G12 = H / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / Ph (opt. substd.) /
cycloalkyl <containing 3-8 C> / F / Cl / Br / I / CN /
alkylthio <containing 1-10 C>
G13 = O / C(O) / S / alkylene <containing 1-4 C,
unbranched> (opt. substd. by 1 or more G15) / G16 / NH / 16



G14 = Ph (opt. substd. by G36) /
 heteroaryl <containing 1-4 heteroatoms, zero or more N,
 zero or more O, zero or more S (no other heteroatoms),
 monocyclic> / heterocycle <containing 3-8 atoms,
 1-3 heteroatoms, zero or more N, zero or more O,
 zero or more S (no other heteroatoms), monocyclic> /
 cycloalkyl <containing 3-8 C> /
 (Specifically claimed: furyl / imidazolyl / isoxazolyl /
 isothiazolyl / oxadiazolyl / oxazolyl / pyrazinyl /
 pyrazolyl / pyridazinyl / 75 / pyridyl / pyrimidinyl /
 pyrrolyl / tetrazolyl / thiadiazolyl / thiazolyl / thienyl /
 triazinyl / triazolyl / hexahydroazepino / 82 / 91 / 93 /
 azetidino / 101 / 107 / aziridino / 112 / 117 / 124 / 132 /
 148 / 156 / morpholino / 159 / 166 / piperazino / 173 /
 piperidino / 186 / 187 / 194 / pyrrolidino / 206 / 211 /
 heterocycle <containing 1 heteroatom, 1 N, 4 C,
 non-aromatic, 1 double-exact bond,
 5-membered monocyclic ring> / thiomorpholino / 215 / 219 /
 229 / 234 / 239)

G33=O
 75



- G15 = OH / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F
- G16 = (1-4) CH₂
- G17 = alkyl <containing 1-10 C>
- G19 = alkylene <containing 1-4 C, unbranched>
(opt. substd. by 1 or more G15) / G16
- G20 = H / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / F / Cl / Br / I / CN /
alkylthio <containing 1-10 C>
- G21 = H / Me / alkoxy <containing 1-10 C> / F / Cl / Br /
I / CN
- G22 = alkylene <containing 2-6 C>
(opt. substd. by 1 or more G10) / G23
- G23 = (2-6) CH₂
- G24 = alkyl <containing 1-10 C>
(opt. substd. by 1 or more G25) /
cycloalkyl <containing 3-8 C> / (Specifically claimed: Me /
Et / Pr-i)
- G25 = F / Cl / Br / I / OH / alkoxy <containing 1-10 C> /
cycloalkyl <containing 3-8 C>
- G26 = H / alkyl <containing 1-10 C> (substd. by OH) /
alkyl <containing 1-10 C> (substd. by 1 or more F) / OH /
alkyl <containing 1-10 C> / alkoxy <containing 1-10 C> /
alkylamino <containing 1-10 C> /
dialkylamino <each alkyl containing 1-10 C>
- G27 = H / OH / alkyl <containing 1-10 C>
(opt. substd. by OH) / F
- G28 = H / alkyl <containing 1-10 C> (opt. substd. by OH) /
alkyl <containing 1-10 C> (substd. by 1 or more F)
- G29 = (1-5) 57

G30—₅₇C—G30

- G30 = H / OH / alkyl <containing 1-10 C> /
alkoxy <containing 1-10 C> / alkylamino <containing 1-10 C> /
dialkylamino <each alkyl containing 1-10 C> / F /
(Specifically claimed: Me / Et / Pr-i / Bu-i / CH₂OH / NHMe /
NMe₂ / 248)

H₂C—₂₄₈F

- G31 = bond / O / S / 73

₇₃N—G32

- G32 = H / alkyl <containing 1-10 C> /
alkylcarbonyl <containing 1-10 C> / CONH₂ / CHO /
alkylaminocarbonyl <containing 1-10 C> /
dialkylaminocarbonyl <each alkyl containing 1-10 C>
- G33 = heterocycle <containing 2 heteroatoms, 2 N, 4 C,
6-membered monocyclic ring>
- G34 = O / S
- G35 = Me / Et / Pr-i / Bu-i / CH₂OH / 250

H₂C—F
250

G36 = R / Cl / CN / F / SMe

Patent location: claim 1

Note: substitution is restricted

Note: or pharmaceutically acceptable salts, esters, amides, or prodrugs

L52 ANSWER 12 OF 14 MARPAT COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 137:338133 MARPAT

TITLE: Preparation of folate mimetics and folate-receptor binding conjugates thereof

INVENTOR(S): Green, Mark A.; Leamon, Christopher P.; Ke, Chun-Yen

PATENT ASSIGNEE(S): Purdue Research Foundation, USA; Endocyte, Inc.

SOURCE: PCT Int. Appl., 52 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

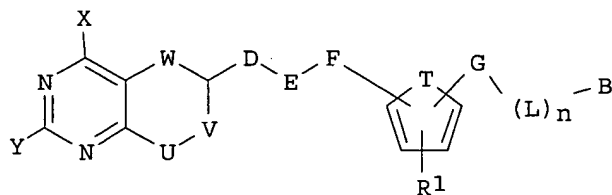
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FAMILY ACC. NUM. COUNT: 1

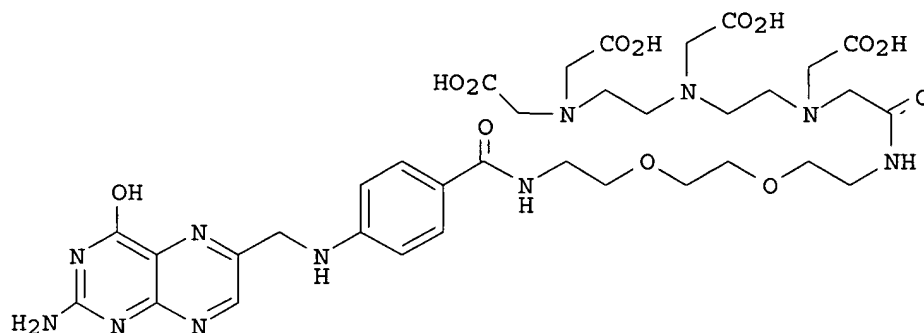
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--|----------|-----------------|----------|
| WO 2002085908 | A1 | 20021031 | WO 2002-US13045 | 20020424 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| EP 1389209 | A1 | 20040218 | EP 2002-731495 | 20020424 |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | |
| US 2004242582 | A1 | 20041202 | US 2004-475876 | 20040621 |
| US 2005227985 | A9 | 20051013 | | |
| PRIORITY APPLN. INFO.: | | | US 2001-286082P | 20010424 |
| | | | WO 2002-US13045 | 20020424 |

GI



I

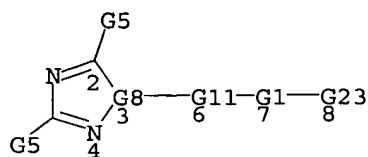


II

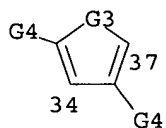
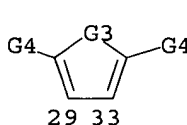
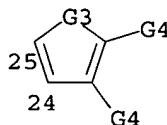
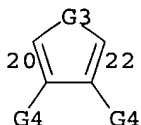
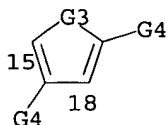
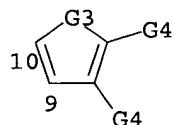
AB A cell population expressing folate receptors is selectively targeted with folate mimetic I [D = (CR6R7)s; E = (A1)p; F = (CR6R7)1-s; G = (A2)r; X, Y = halo, R2, OR2, SR3, NR4R5; U, V, W = (R6')C:, N:, (R6')C(R7'), N(R4'); T = S, O, N, C:C (such that T is part of an aromatic ring); A1, A2 = C(Z), C(Z)O, OC(Z), N(R4''), C(Z)N(R4''), N(R4'')C(Z), OC(Z)N(R4''), N(R4'')C(Z)O, N(R4'')C(Z)N(R5''), O, S, S(O), SO2, N(R4'')SO2, C(R6'')C(R7''), N(C.tplbond.CH), N(CH2C.tplbond.CH), C1-12-alkyl, C1-12-alkoxy; Z = O, S; R1 = H, halo, C1-12-alkyl, C1-12-alkoxy; R2 - R5, R4', R4'' - R7'' = H, halo, C1-12-alkyl, C1-12-alkoxy, C1-12-alkenyl, C1-12-alkynyl, (C1-12-alkoxy)carbonyl, (C1-12-alkylamino)carbonyl; R6, R7 = H, halo, C1-12-alkyl, C1-12-alkoxy; R6R7 = O; R6', R7' = H, halo, C1-12-alkyl, C1-12-alkoxy; R6'R7' = O; L = divalent linker (with the proviso that L ≠ naturally occurring amino acid covalently linked to A2 at its α-amino group through an amide bond); n, p, r, s = 0, 1; B = H, leaving group]. Thus, CYK4-013 (II) was prepared from pterioic acid via coupling with (CH2OCH2CH2NH2)2 using PyBOP, HOBt and N-methylmorpholine in DMSO, followed by addition of DTPA tris(tert-butyl) ester. The folate mimetic is conjugated to a diagnostic or therapeutic agent to enable selective delivery of the agent to the targeted cell population. The ¹¹¹In complex of II was selectively localized in the folate-receptor-pos. tumor xenografts of human KB cells in athymic mice (NuNu strain) and afforded prolonged tumor retention of ¹¹¹In (5.4, 5.5, and 3.6% ID/g at 1 h, 4 h, and 24 h, resp.); blockable binding was also observed in the kidneys, where the folate receptor occurs in the proximal tubes.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

MSTR 1



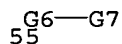
G1 = phenylene (opt. substd. by 1 or more G2) /
 10-6 9-8 / 15-6 18-8 / 20-6 22-8 / 24-6 25-8 /
 29-6 33-8 / 34-6 37-8



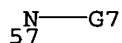
G2 = F / Cl / Br / I / At / alkyl <containing 1-12 C> /
 alkoxy <containing 1-12 C> / (Specifically claimed: Me)
 G3 = S / O / 51



G4 = H / F / Cl / Br / I / At /
 alkyl <containing 1-12 C> / alkoxy <containing 1-12 C> /
 (Specifically claimed: Me)
 G5 = F / Cl / Br / I / At / H /
 alkyl <containing 1-12 C> / alkoxy <containing 1-12 C> /
 CHO / alkylcarbonyl <containing 1-11 C> /
 alkenyl <containing 2-12 C> / alkynyl <containing 2-12 C> /
 alkoxy carbonyl <containing 1-12 C> /
 alkylaminocarbonyl <containing 1-12 C> /
 dialkylaminocarbonyl <each alkyl containing 1-12 C> / 55 /
 (Specifically claimed: Me)



G6 = O / S / 57

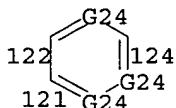


G7 = H / F / Cl / Br / I / At /
 alkyl <containing 1-12 C> / alkoxy <containing 1-12 C> /

CHO / alkylcarbonyl <containing 1-11 C> /
 alkenyl <containing 2-12 C> / alkynyl <containing 2-12 C> /
 alkoxycarbonyl <containing 1-12 C> /
 alkylaminocarbonyl <containing 1-12 C> /
 dialkylaminocarbonyl <each alkyl containing 1-12 C> /
 (Specifically claimed: Me)

G8 = any ring <containing 0-3 heteroatoms,
 0-3 N (no other heteroatoms), 3 or more C,
 1 or more double bonds, attached through 3 or more C,
 6-membered monocyclic ring> (opt. substd. by 1 or more G9) /
 59 / (Specifically claimed: 122-2 121-4 124-6)

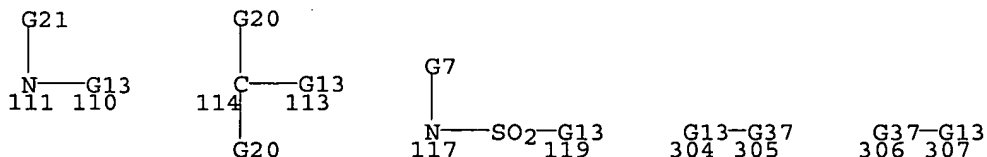
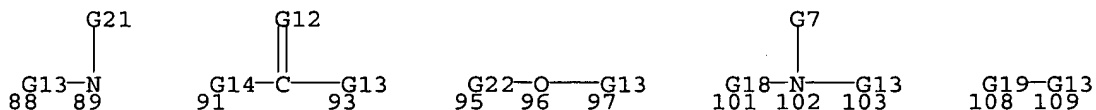
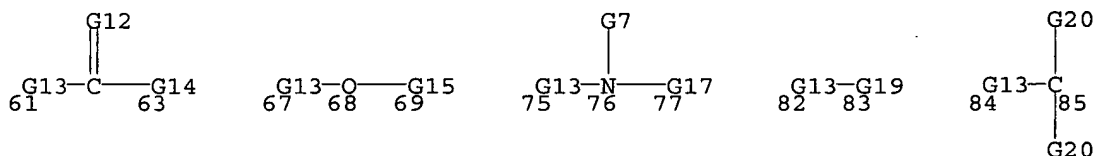
G10=O
 59



G9 = F / Cl / Br / I / At / alkyl <containing 1-12 C> /
 alkoxy <containing 1-12 C> / CHO /
 alkylcarbonyl <containing 1-11 C> /
 alkenyl <containing 2-12 C> / alkynyl <containing 2-12 C> /
 alkoxycarbonyl <containing 1-12 C> /
 alkylaminocarbonyl <containing 1-12 C> /
 dialkylaminocarbonyl <each alkyl containing 1-12 C>

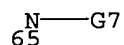
G10 = any ring <containing 0-2 heteroatoms,
 0-2 N (no other heteroatoms), 4 or more C,
 1 or more double bonds, attached through 4 or more C,
 6-membered monocyclic ring> (opt. substd.)

G11 = CH2 (opt. substd.) / C(O) / 61-3 63-7 /
 67-3 69-7 / 75-3 77-7 / 82-3 83-7 / 84-3 85-7 /
 88-3 89-7 / 91-3 93-7 / 95-3 97-7 / 101-3 103-7 /
 108-3 109-7 / 111-3 110-7 / 114-3 113-7 / 117-3 119-7 /
 304-3 305-7 / 306-3 307-7 / 308-3 310-7 / 311-3 313-7 /
 314-3 316-7 / 317-3 319-7

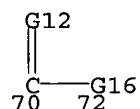




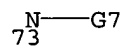
G12 = O / S
 G13 = CH2 (opt. substd.) / C(O)
 G14 = bond / O / 65



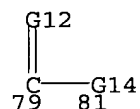
G15 = 70-68 72-7 / bond



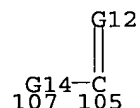
G16 = bond / 73



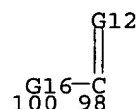
G17 = bond / 79-76 81-7 / SO2



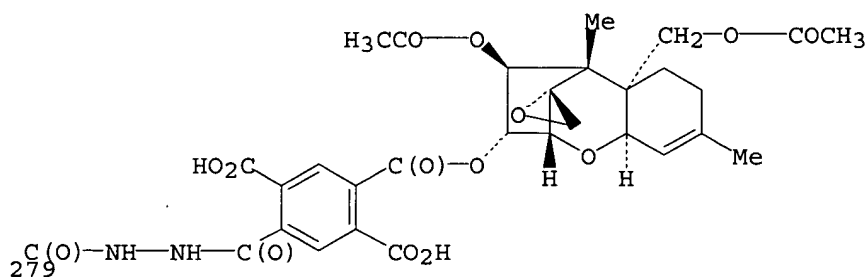
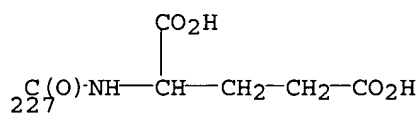
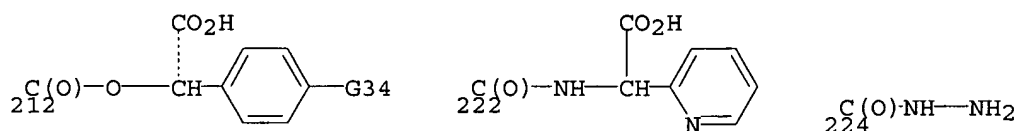
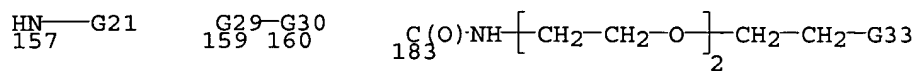
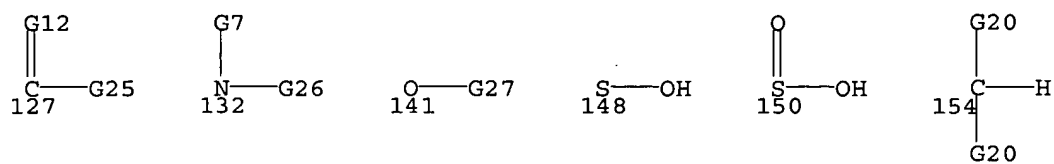
G18 = bond / 107-3 105-102



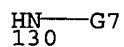
G19 = S / S(O) / SO2
 G20 = H / R / (Specifically claimed: Me)
 G21 = ethynyl / propargyl
 G22 = 100-3 98-96 / bond



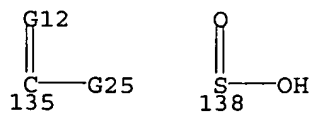
G23 = H / R <"leaving or linking group,
 or diagnostic or therapeutic agent"> / 127 / 132 / 141 / SH /
 148 / 150 / 154 / 157 / alkyl <containing 1-12 C>
 (opt. substd. by OH) / alkoxy <containing 1-12 C> / 159 /
 (Examples: 183 / 212 / 222 / 224 / 227 / 279)



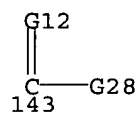
G24 = CH / N
 G25 = H / OH / 130



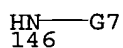
G26 = H / 135 / 138



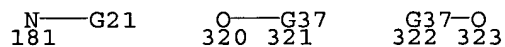
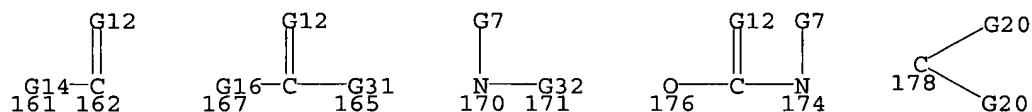
G27 = 143 / H



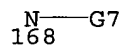
G28 = H / 146



G29 = 161-7 162-160 / 167-7 165-160 / 170-7 171-160 /
176-7 174-160 / O / S / S(O) / SO2 / 178 / 181 /
alkylene <containing 1-12 C> / 320-7 321-160 /
322-7 323-160

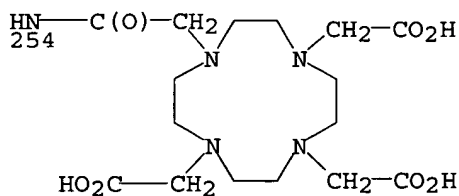
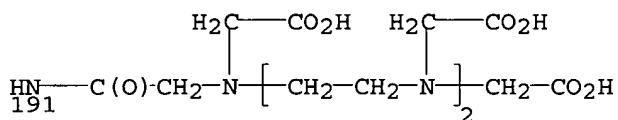


G30 = R <"leaving or linking group,
or diagnostic or therapeutic agent">
G31 = O / 168

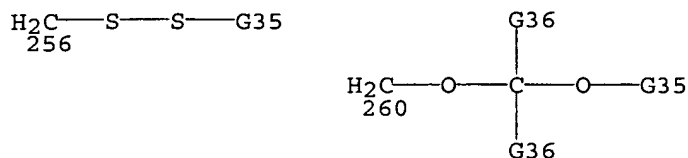


G32 = bond / SO2

G33 = 191 / 254



G34 = H / 256 / 260



G35 = R <"drug or drug bearing moiety">
 G36 = H / alkyl / cycloalkyl / Ph (substd.)
 G37 = alkylene <containing 1-12 C>
 Patent location: claim 1
 Note: also incorporates claim 9
 Note: substitution is restricted

L52 ANSWER 13 OF 14 MARPAT COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 132:30857 MARPAT
 TITLE: Heterocyclic compound inhibitors of p38 kinase, pharmaceutical compositions, and therapeutic use
 INVENTOR(S): Salituro, Francesco; Bemis, Guy; Cochran, John
 PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA
 SOURCE: PCT Int. Appl., 68 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

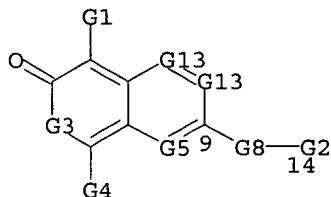
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 9964400 | A1 | 19991216 | WO 1999-US12951 | 19990611 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 9944297 | A1 | 19991230 | AU 1999-44297 | 19990611 |
| EP 1086085 | A1 | 20010328 | EP 1999-927377 | 19990611 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| EP 1277740 | A1 | 20030122 | EP 2002-22891 | 19990611 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY | | | | |
| US 2001025044 | A1 | 20010927 | US 2000-734069 | 20001211 |
| US 6528508 | B2 | 20030304 | | |
| US 2003149037 | A1 | 20030807 | US 2002-327020 | 20021220 |
| US 6800626 | B2 | 20041005 | | |
| US 2005049251 | A1 | 20050303 | US 2004-951409 | 20040927 |
| PRIORITY APPLN. INFO.: | | | | |
| | | | US 1998-89147P | 19980612 |
| | | | EP 1999-927377 | 19990611 |
| | | | WO 1999-US12951 | 19990611 |
| | | | US 2000-734069 | 20001211 |
| | | | US 2002-327020 | 20021220 |

AB The invention relates to heterocyclic compound inhibitors of p38, a

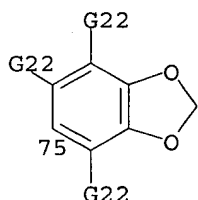
mammalian protein kinase involved cell proliferation, cell death and response to extracellular stimuli. The invention also relates to methods for producing these inhibitors. The invention also provides pharmaceutical compns. comprising the inhibitors of the invention and methods of utilizing those compns. in the treatment and prevention of various disorders.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

MSTR 1A



G1 = Ph (opt. substd.) / heterocycle <containing 5-6 atoms, aromatic, 5- to 6-membered monocyclic ring> (opt. substd.) / aryl <containing 8-10 C, bicyclic> (opt. substd.) / heterocycle <containing 8-10 atoms, aromatic, bicyclic> (opt. substd.) / (Specifically claimed: Ph (opt. substd. by (1-3) G17) / pyridyl (opt. substd. by (1-3) G17) / 75)

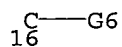


G2 = Ph (opt. substd.) / heterocycle <containing 5-6 atoms, aromatic, 5- to 6-membered monocyclic ring> (opt. substd.) / aryl <containing 8-10 C, bicyclic> (opt. substd.) / heterocycle <containing 8-10 atoms, aromatic, bicyclic> (opt. substd.) / (Specifically claimed: Ph (opt. substd. by (1-3) G20) / pyridyl (opt. substd. by (1-3) G20))

G3 = O / NH (opt. substd.)

G4 = H / alkyl <containing 1-3 C> / OH / alkoxy <containing 1-3 C>

G5 = N / 16

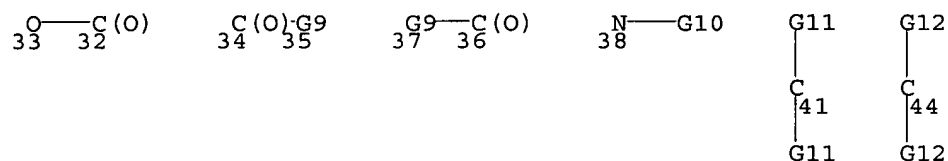
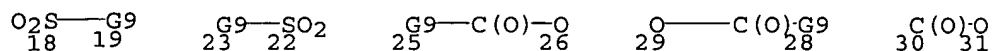


G6 = H / alkyl <containing 1-3 C> / alkenyl <containing 2-3 C> / alkynyl <containing 2-3 C> / Ph (opt. substd. by (1-3) G7)

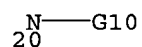
G7 = halo / OMe / CN / NO2 / NH2 / OH / Me / Et

G8 = S / O / SO2 / S(O) / 18-9 19-14 / 23-9 22-14 /

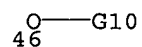
25-9 26-14 / 29-9 28-14 / C(O) / 30-9 31-14 /
 33-9 32-14 / 34-9 35-14 / 37-9 36-14 / NH / 38 / 41 / 44



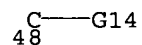
G9 = NH / 20



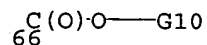
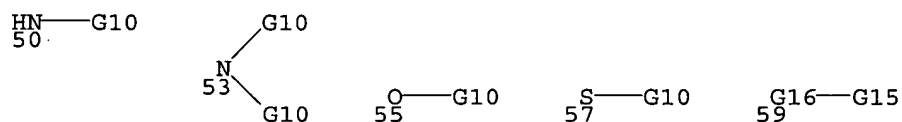
G10 = alkyl <containing 1-3 C> (opt. substd.) /
 alkenyl <containing 2-3 C> (opt. substd.)
 G11 = H / alkyl <containing 1-3 C> (opt. substd.) /
 alkenyl <containing 2-3 C> (opt. substd.)
 G12 = OH / 46



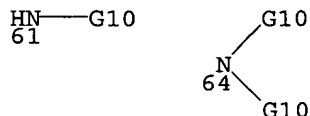
G13 = N / 48



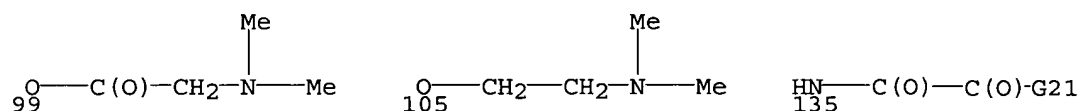
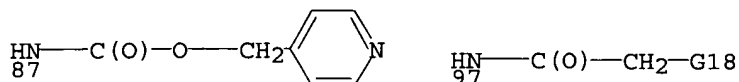
G14 = H / alkyl <containing 1-3 C> (opt. substd.) /
 alkenyl <containing 2-3 C> (opt. substd.) / NH2 / 50 / 53 /
 OH / 55 / SH / 57 / 59 / CO2H / 66 /
 (Specifically claimed: Me)



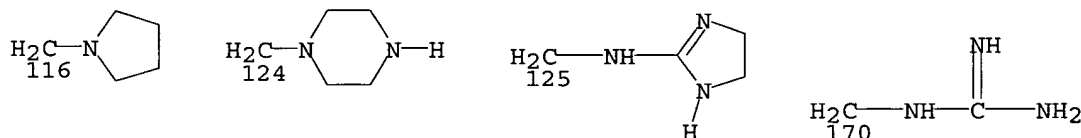
G15 = NH2 / 61 / 64



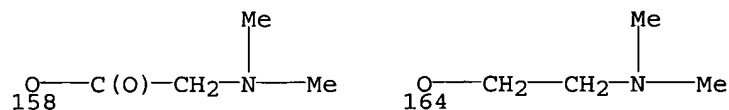
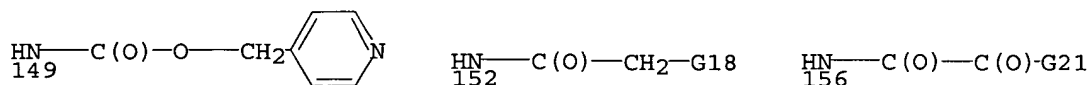
G16 = C(O) / SO₂
 G17 = Cl / F / Br / Me / OMe / OH / CF₃ / OCF₃ / OPr-n /
 NH₂ / NMe₂ / NHSO₂Ph / 87 / 97 / 135 / 99 / 105



G18 = morpholino / NMe₂ / piperazino / pyrrolidino
 G20 = Cl / F / Br / Me / Et / Pr-i / OMe / OH / NH₂ /
 CF₃ / OCF₃ / SMe / OMe / CO₂H / CO₂Me / CH₂NH₂ / NMe₂ / 116 /
 CH₂OH / (Specifically claimed: 124 / NHC(NH)NH₂ / 170 / 125)



G21 = morpholino / piperazino / pyrrolidino
 G22 = H / Cl / F / Br / Me / OMe / OH / CF₃ / OCF₃ /
 OPr-n / NH₂ / NMe₂ / NHSO₂Ph / 149 / 152 / 156 / 158 / 164



Derivative:
 Patent location:
 Note:

or pharmaceutically acceptable salts
 claim 1
 additional ring formation also claimed

L52 ANSWER 14 OF 14 MARPAT COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 129:54361 MARPAT
 TITLE: Preparation of benzisothiazolones and analogs as
 α1C-adrenergic receptor antagonists

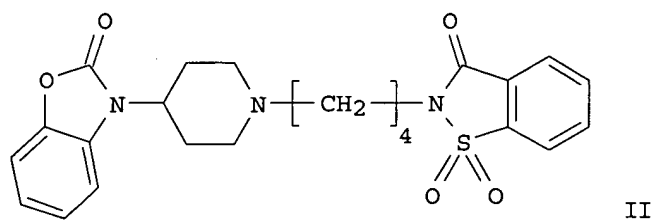
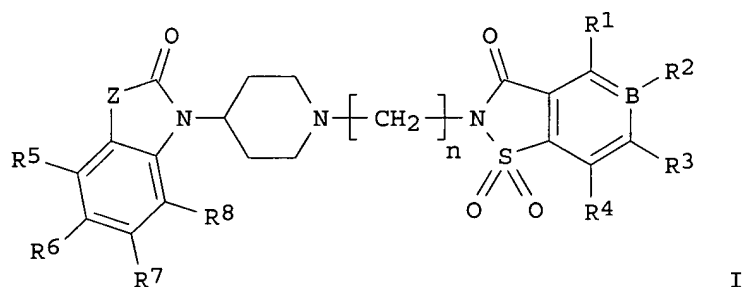
INVENTOR(S): Huff, Joel R.; Lee, Hee-yoon; Nerenberg, Jennie B.;
Thompson, Wayne J.; Bell, Ian M.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: U.S., 57 pp., Cont.-in-part of U. S. Ser. No. 229,276,
abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|------|----------|-----------------|----------|
| US 5760054 | A | 19980602 | US 1996-722001 | 19961001 |
| WO 9528397 | A1 | 19951026 | WO 1995-US4590 | 19950413 |

W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TT, UA, US, UZ
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1994-229276 19940413
WO 1995-US4590 19950413

GI



AB The invention relates to the claimed title compds. I [n = 3-5; B = C or N; R1, R2, R3, R4 = H, halo, NO2, NH2, (un)substituted alkyl, alkoxy, aryl, heteroaryl, etc.; R5, R6, R7, R8 = H, alkyl, alkenyl, alkoxy; Z = O, S, CH2, NH, NMe] and analogs. Also disclosed are the synthesis and use of the compds. as selective α 1C-adrenergic receptor antagonists. The primary application of the compds. is in the treatment of benign prostatic

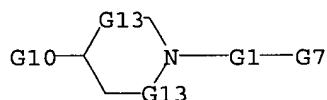
hypertrophy (BPH). The compds. selectively relax smooth muscle tissue enriched in the $\alpha 1C$ receptor subtype without inducing orthostatic hypotension. The compds. provide acute relief of BPH by permitting less hindered urine flow. I and analogs are also useful in combination with human 5α -reductase inhibitors, providing both acute and chronic relief from the effects of BPH. Approx. 130 specific invention compds. are disclosed. The cloning and use of a cDNA for a human $\alpha 1C$ adrenoceptor in an in vitro assay is described. For instance, alkylation of 1-(4-piperidinyl)-3-benzoxazolin-2-one.HCl (prepared in 4 steps) with 2-(4-bromobutyl)-1,1-dioxido-1,2-benzisothiazol-3(2H)-one in the presence of (i-Pr)₂NEt in DMF gave 40% title compound II. Selected compds. showed nanomolar or subnanomolar affinity for human $\alpha 1C$ receptor subtype while showing 30-fold lower affinity for human $\alpha 1A$ and $\alpha 1B$ subtypes (no data).

REFERENCE COUNT:

3

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

MSTR 2C

G1 = (3-5) CH₂

G3 = H / halo / NO₂ / NH₂ /
alkyl <containing 1-8 C> (opt. substd. by 1 or more G4) /
alkoxy <containing 1-8 C> (opt. substd.) /
alkylsulfonyl <containing 1-8 C> / aryl (opt. substd.) /
heteroaryl (opt. substd.)

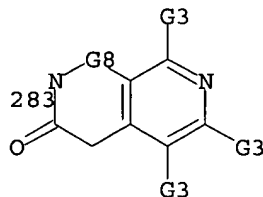
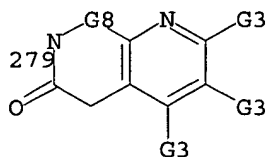
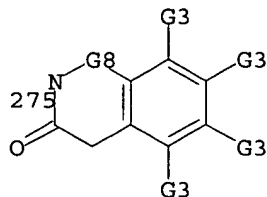
G4 = halo / CF₃ / alkyl / alkoxy / aryl / heteroaryl

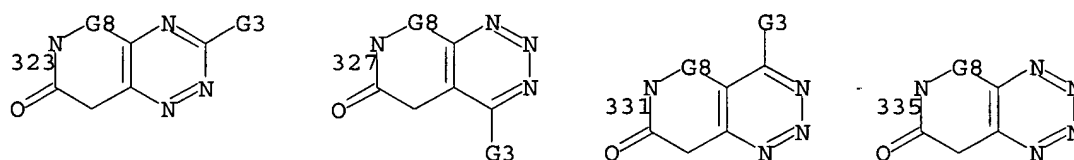
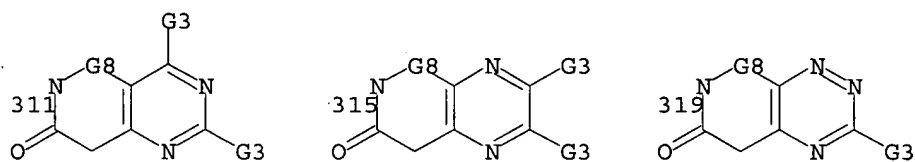
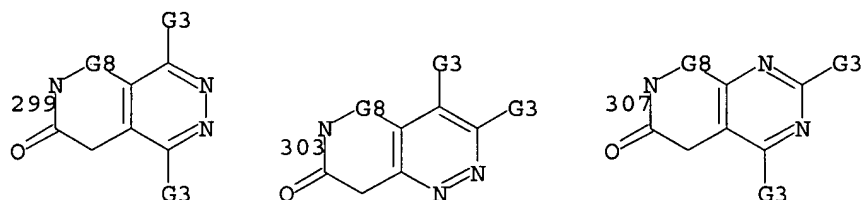
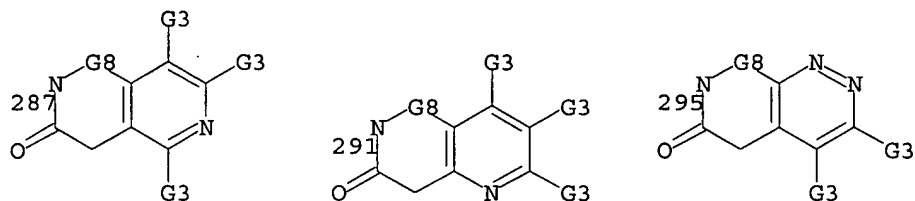
G5 = H / alkyl <containing 1-8 C> /
alkenyl <containing 2-8 C> / alkoxy <containing 1-8 C>

G6 = O / S / CH₂ / NH / NMe / 269-21 270-23 /
271-21 272-23 / carbon chain <containing 1-8 C,
0 or more double bonds, no triple bonds>

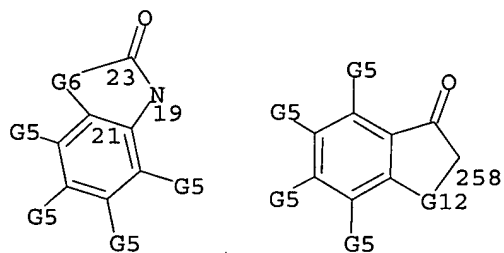


G7 = 275 / 279 / 283 / 287 / 291 / 295 / 299 / 303 /
307 / 311 / 315 / 319 / 323 / 327 / 331 / 335





G8 = C(O) / SO₂
 G10 = 19 / 258



G11 = O / S
 G12 = NH / CH₂ / carbon chain <containing 1-3 C,
 0 or more double bonds, no triple bonds>
 G13 = G14 / NH / S / O
 G14 = (0-3) CH₂

Derivative:

and pharmaceutically acceptable salts, prodrugs,
 polymorphs, or metabolites

Patent location:

disclosure

Search history

Jaisle 10/824980

07/19/2006

=> d his full

(FILE 'HOME' ENTERED AT 13:39:22 ON 19 JUL 2006)

FILE 'REGISTRY' ENTERED AT 13:39:28 ON 19 JUL 2006

L1 STRUCTURE UPLOADED
L2 1 SEA SSS SAM L1
D SCA
D L1

FILE 'STNGUIDE' ENTERED AT 13:41:36 ON 19 JUL 2006

FILE 'REGISTRY' ENTERED AT 13:42:21 ON 19 JUL 2006

L3 STRUCTURE UPLOADED
L4 1 SEA SSS SAM L3
L5 7 SEA SSS FUL L3
SAVE TEMP L5 JAI980STRB/A

FILE 'HCAPLUS' ENTERED AT 13:43:48 ON 19 JUL 2006

L6 2 SEA ABB=ON PLU=ON L5

FILE 'STNGUIDE' ENTERED AT 13:43:57 ON 19 JUL 2006

FILE 'BEILSTEIN' ENTERED AT 13:46:08 ON 19 JUL 2006

L7 0 SEA SSS SAM L3
L8 0 SEA SSS FUL L3

FILE 'BEILSTEIN' ENTERED AT 13:46:40 ON 19 JUL 2006

D STAT QUE L8

FILE 'HCAPLUS' ENTERED AT 13:47:37 ON 19 JUL 2006

E US2004-824980/APPS
L9 1 SEA ABB=ON PLU=ON US2004-824980/AP
D SCA L9
SEL RN

FILE 'REGISTRY' ENTERED AT 13:48:17 ON 19 JUL 2006

L10 16 SEA ABB=ON PLU=ON (165245-96-5/BI OR 23056-33-9/BI OR
367-27-1/BI OR 402927-97-3/BI OR 777899-52-2/BI OR 777899-53-3/
BI OR 777899-54-4/BI OR 777899-55-5/BI OR 777899-56-6/BI OR
777899-57-7/BI OR 777899-58-8/BI OR 777899-59-9/BI OR 777899-60
-2/BI OR 777899-61-3/BI OR 777899-62-4/BI OR 777899-63-5/BI)

L11 5 SEA ABB=ON PLU=ON L10 AND L5
L12 11 SEA ABB=ON PLU=ON L10 NOT L11
D SCA

L13 ANALYZE PLU=ON L5 1- LC : 3 TERMS
D

FILE 'STNGUIDE' ENTERED AT 13:50:47 ON 19 JUL 2006

FILE 'MARPAT' ENTERED AT 13:52:35 ON 19 JUL 2006

L14 4 SEA SSS SAM L3
L15 54 SEA SSS FUL L3

FILE 'STNGUIDE' ENTERED AT 13:53:09 ON 19 JUL 2006

FILE 'MARPAT' ENTERED AT 13:53:13 ON 19 JUL 2006

SAVE TEMP L15 JAI980MARB/A

FILE 'STNGUIDE' ENTERED AT 13:54:27 ON 19 JUL 2006

FILE 'MARPAT' ENTERED AT 13:56:11 ON 19 JUL 2006
L16 STRUCTURE UPLOADED
L17 3 SEA SUB=L15 SSS SAM L16
L18 39 SEA SUB=L15 SSS FUL L16
SAVE TEMP L18 JAI980MARPC/A

FILE 'STNGUIDE' ENTERED AT 14:04:18 ON 19 JUL 2006

FILE 'REGISTRY' ENTERED AT 14:12:28 ON 19 JUL 2006

FILE 'MARPAT' ENTERED AT 14:12:50 ON 19 JUL 2006
L19 STRUCTURE UPLOADED
L20 2 SEA SUB=L15 SSS SAM L19
L21 13 SEA SUB=L15 SSS FUL L19
D SCA

FILE 'STNGUIDE' ENTERED AT 14:17:17 ON 19 JUL 2006

FILE 'MARPAT' ENTERED AT 14:17:45 ON 19 JUL 2006
SAVE TEMP L21 JAI980MARPD/A
L22 STRUCTURE UPLOADED
L23 1 SEA SUB=L15 SSS SAM L22
D SCA
L24 2 SEA SUB=L15 SSS FUL L22
D SCA
SAVE TEMP L24 JAI980MARPE/A
D COST

FILE 'WPIX' ENTERED AT 14:23:43 ON 19 JUL 2006
L25 2 SEA SSS SAM L3
D SCA
L26 5 SEA SSS FUL L3
L27 1 SEA ABB=ON PLU=ON L26/DCR
SEL SDCN L26
EDIT E17-E21 /SDCN /DCN
L28 1 SEA ABB=ON PLU=ON (RAFUWH/DCN OR RAFUWI/DCN OR RAFUWJ/DCN OR
RAFUWK/DCN OR RAFUWL/DCN)
SEL DCSE L26
L29 1 SEA ABB=ON PLU=ON (979788-1-0-0/DCRE OR 979789-0-0-0/DCRE OR
979790-0-0-0/DCRE OR 979791-0-0-0/DCRE OR 979792-0-0-0/DCRE)
L30 1 SEA ABB=ON PLU=ON L28 OR L29
D SCA

FILE 'STNGUIDE' ENTERED AT 14:27:01 ON 19 JUL 2006

FILE 'HCAPLUS' ENTERED AT 14:27:50 ON 19 JUL 2006
L31 12 SEA ABB=ON PLU=ON DEWDNEY N?/AU
L32 1091 SEA ABB=ON PLU=ON GOLDSTEIN D?/AU
L33 3 SEA ABB=ON PLU=ON L31 AND L32
L34 1 SEA ABB=ON PLU=ON (L31 OR L32) AND L6
L35 23 SEA ABB=ON PLU=ON (L31 OR L32) AND (P38/OBI OR P 38/OBI)

FILE 'MARPAT' ENTERED AT 14:30:46 ON 19 JUL 2006
L36 0 SEA ABB=ON PLU=ON DEWDNEY N?/AU
L37 4 SEA ABB=ON PLU=ON L31
L38 20 SEA ABB=ON PLU=ON L32
L39 1 SEA ABB=ON PLU=ON (L37 OR L38) AND (L21 OR L24)

FILE 'WPIX' ENTERED AT 14:32:44 ON 19 JUL 2006

L40 4 SEA ABB=ON PLU=ON DEWDNEY N?/AU
L41 97 SEA ABB=ON PLU=ON GOLDSTEIN D?/AU
L42 3 SEA ABB=ON PLU=ON L40 AND L41
L43 1 SEA ABB=ON PLU=ON (L40 OR L41) AND L30

FILE 'STNGUIDE' ENTERED AT 14:33:31 ON 19 JUL 2006
D COST

INDEX 'ABI-INFORM, ADISCTI, AEROSPACE, AGRICOLA, ALUMINIUM, ANABSTR,
ANTE, APOLLIT, AQUALINE, AQUASCI, AQUIRE, BABS, BIBLIODATA, BIOENG,
BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAOLD, CAPLUS, CASREACT,
CBNB, CEABA-VTB, CERAB, CHEMINFORMRX, CHEMSAFE, ...' ENTERED AT 14:35:22
ON 19 JUL 2006

SEA (DEWDNEY N?/AU) AND (GOLDSTEIN D?/AU)

3 FILE CAPLUS
0* FILE CBNB
0* FILE CIN
3 FILE DPCI
3 FILE EPFULL
0* FILE IFICLS
3 FILE IFIPAT
0* FILE IMSDRUGNEWS
12 FILE INPADOC
0* FILE NLDB
0* FILE NUTRACEUT
0* FILE PATDPA
0* FILE PATDPASPC
3 FILE PCTFULL
0* FILE PCTGEN
0* FILE PHARMAML
0* FILE PHIC
0* FILE PHIN
0* FILE RDISCLOSURE
3 FILE USPATFULL
3 FILE WPIDS
3 FILE WPINDEX

L44 QUE ABB=ON PLU=ON (DEWDNEY N?/AU) AND (GOLDSTEIN D?/AU)

FILE 'HCAPLUS' ENTERED AT 14:37:29 ON 19 JUL 2006
D SCA TI L35

FILE 'STNGUIDE' ENTERED AT 14:38:30 ON 19 JUL 2006

FILE 'REGISTRY' ENTERED AT 14:38:41 ON 19 JUL 2006

FILE 'HCAPLUS' ENTERED AT 14:38:45 ON 19 JUL 2006

D STAT QUE L33
D STAT QUE L34
D STAT QUE L35

L45 23 SEA ABB=ON PLU=ON (L33 OR L34 OR L35)

FILE 'MARPAT' ENTERED AT 14:39:29 ON 19 JUL 2006
D STAT QUE L39

FILE 'WPIX' ENTERED AT 14:40:18 ON 19 JUL 2006

D STAT QUE L42
D STAT QUE L43

L46 3 SEA ABB=ON PLU=ON (L42 OR L43)

FILE 'STNGUIDE' ENTERED AT 14:40:45 ON 19 JUL 2006

FILE 'HCAPLUS, WPIX, MARPAT' ENTERED AT 14:41:05 ON 19 JUL 2006

L47 24 DUP REM L45 L46 L39 (3 DUPLICATES REMOVED)
ANSWERS '1-23' FROM FILE HCAPLUS
ANSWER '24' FROM FILE WPIX
D IBIB ABS HITIND HITSTR L47 1-23
D IBIB ABS HITSTR L47 24

FILE 'STNGUIDE' ENTERED AT 14:42:26 ON 19 JUL 2006

FILE 'REGISTRY' ENTERED AT 14:42:43 ON 19 JUL 2006

L48 D STAT QUE L6
7 SEA ABB=ON PLU=ON L6 NOT L45
D COST

FILE 'HCAPLUS' ENTERED AT 14:44:59 ON 19 JUL 2006

L49 D STAT QUE L6
1 SEA ABB=ON PLU=ON L6 NOT L45

FILE 'WPIX' ENTERED AT 14:45:43 ON 19 JUL 2006

L50 D STAT QUE L30
0 SEA ABB=ON PLU=ON L30 NOT L46

FILE 'MARPAT' ENTERED AT 14:46:10 ON 19 JUL 2006

L51 D STAT QUE L21
D STAT QUE L24
13 SEA ABB=ON PLU=ON (L21 OR L24) NOT L39

FILE 'BEILSTEIN' ENTERED AT 14:47:23 ON 19 JUL 2006

D STAT QUE L8

FILE 'HCAPLUS, MARPAT' ENTERED AT 14:47:53 ON 19 JUL 2006

L52 14 DUP REM L49 L50 L51 L8 (0 DUPLICATES REMOVED)
ANSWER '1' FROM FILE HCAPLUS
ANSWERS '2-14' FROM FILE MARPAT
D IBIB ABS HITIND HITSTR L52 1
D IBIB ABS HIT L52 2-14

FILE 'STNGUIDE' ENTERED AT 14:50:31 ON 19 JUL 2006

FILE HOME

FILE REGISTRY

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 18 JUL 2006 HIGHEST RN 894196-03-3

DICTIONARY FILE UPDATES: 18 JUL 2006 HIGHEST RN 894196-03-3

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and

predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/regprops.html>

FILE STNGUIDE

FILE CONTAINS CURRENT INFORMATION.

LAST RELOADED: Jul 17, 2006 (20060717/UP).

FILE HCAPLUS

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FILE COVERS 1907 - 19 Jul 2006 VOL 145 ISS 4

FILE LAST UPDATED: 18 Jul 2006 (20060718/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE BEILSTEIN

FILE LAST UPDATED ON JUNE 16, 2006

FILE COVERS 1771 TO 2006.

FILE CONTAINS 9,606,495 SUBSTANCES

>>>PLEASE NOTE: Reaction Data and substance data are stored in separate documents and can not be searched together in one query. Reaction data for BEILSTEIN compounds may be displayed immediately with the display codes PRE (preparations) and REA (reactions). A substance answer set retrieved after the search for a chemical name, a compounds with available reaction information by combining with PRE/FA, REA/FA or more generally with RX/FA. The BEILSTEIN Registry Number (BRN) is the link between a BEILSTEIN compound and belonging reactions. For more detailed reaction searches BRNs can be searched as reaction partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE <<<

* PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST. *
* SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE *
* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE *
* ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS. *
* FOR PRICE INFORMATION SEE HELP COST *

NEW

* PATENT NUMBERS (PN) AND BABS ACCESSION NUMBERS (BABSAN) CAN NOW BE SEARCHED, SELECTED AND TRANSFERRED.

* NEW DISPLAY FORMATS ALLREF, ALLP AND BABSAN SHOW ALL REFERENCES,
ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A
COMPOUND AT A GLANCE.

FILE MARPAT

FILE CONTENT: 1961-PRESENT VOL 145 ISS 1 (20060714/ED)

SOME MARPAT RECORDS ARE DERIVED FROM INPI DATA FOR 1961-1987

MOST RECENT CITATIONS FOR PATENTS FROM MAJOR ISSUING AGENCIES
(COVERAGE TO THESE DATES IS NOT COMPLETE):

| | | |
|----|--------------|-------------|
| US | 2006118302 | 08 JUN 2006 |
| DE | 102004053653 | 04 MAY 2006 |
| EP | 1653548 | 03 MAY 2006 |
| JP | 2006112980 | 27 APR 2006 |
| WO | 2006053912 | 26 MAY 2006 |
| GB | 2419594 | 03 MAY 2006 |
| FR | 2877004 | 28 APR 2006 |
| RU | 2275374 | 27 APR 2006 |
| CA | 2518664 | 10 MAR 2006 |

Expanded G-group definition display now available.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

FILE WPIX

FILE LAST UPDATED: 14 JUL 2006 <20060714/UP>
MOST RECENT DERWENT UPDATE: 200645 <200645/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
<http://scientific.thomson.com/support/patents/coverage/latestupdates/>

>>> PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE
http://www.stn-international.de/stndatabases/details/ipc_reform.html and
<http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf> <<<

>>> FOR FURTHER DETAILS ON THE FORTHCOMING DERWENT WORLD PATENTS
INDEX ENHANCEMENTS PLEASE VISIT:
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<

FILE STNINDEX

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